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Sherlock Holmes and a Racemic Case: A Didactic Proposal to Approach the Enantiomers Class

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Abstract

Sherlock Holmes, the literary character created by Sir Arthur Conan Doyle, is used in this work to illustrate the deductive skills needed in science. Holmes' own story is used to illustrate the use of analogy and to highlight the importance of stereoisomerism and the properties of enantiomers in medical practice.

Subject Areas

Medicine, Organic Chemistry, Therapy

Keywords

Sherlock Holmes, Analogies, Enantiomers, Pharmacology

1. Introduction

The literary character Sherlock Holmes, created by Sir Arthur Conan Doyle, first appeared in the short novel *Study in Scarlet* in 1887. [1] The impact of Mr. Holmes has transcended fictional literature and has given rise to countless series available on internet platforms and cinema films. The most recent is a 2021 film starring actor Robert Downing Jr. as Holmes.

Holmes' deductive skills have also been exploited in science teaching texts. A quick scan of the *PubMed* site with the keywords Sherlock Holmes and science yields more than 40 recent titles. There, the character exemplifies the deductive

skills that are promoted in a researcher or science professional. For years, we have decided to write our own texts with the central character of Sherlock Holmes and his associate Dr Watson [2] [3] [4] [5] [6]. The Sherlock Holmes metaphor is also a creative and flexible tool for therapists in their work with patients [7]. Thus, we can cover curriculum topics not considered by Conan Doyle's original texts. In the following text, we offer the teacher the possibility to exemplify the use of analogies [8] [9] and extend the application, in medical practice, of the concept of a particular type of stereoisomers, the enantiomers. Enantiomers are pairs of compounds with the same substituents, but opposite three-dimensional shapes. They are mirror images of each other. For example, in a tetrahedral atom, such as carbon, with four different groups attached to it, the resulting enantiomers will be two compounds that are mirrors of each other. They cannot be superimposed on each other. In the story generated by us, a scenario analogous to that of the enantiomers is proposed with the characters.

2. The Case of Mr. Keneth Rydeberg

It was an inhospitable winter. We were with Holmes in the Baker Street rooms sheltered by the warmth of the logs.

Holmes was going for his second pipe while I went back to reading a monograph on salts used in medicine.

- Strange, said Holmes

- What is strange, Holmes?

- That someone should be visiting us in this weather.

- But Holmes! I have heard no sound to denote the arrival of a visitor.

A few moments later we heard Mrs. Hudson's footsteps, and then her knock at the door.

- Come in, Mrs. Hudson, shouted Holmes.

True to her professional style, Mrs. Hudson called out:

- Mr. Holmes, a man has come to visit you and asked me if you would be kind enough to listen to him. He says his name is Keneth Rydeberg.

- Well, well, Mrs. Hudson, send him in.

At once a tall man of robust build came into our office. His face showed concern.

- Thank you, Mr. Holmes, for seeing me. I wish to consult you on a matter that has caused me some fear and surprise.

- We are happy to listen to you. Please know that my associate, Dr. Watson, is my most trusted confidant.

- You see, Mr. Holmes. I have a small wine production facility. I live in Mirrortown and our production is sufficient to supply the small community. I have two of my most trusted employees for the production and packaging of the fermentation product, *i.e.* a wine with local characteristics. A fortnight ago a remarkable customer came by our facility and she was accompanied by a cousin. Suddenly, her cousin fainted at the sight of one of my employees. It was young

Marcus Twoson. When she came to, with the help of strong liquor, the cousin mentioned serious accusations against Marcus that implied a total lack of social values. The lady did not feel prudently confident to detail to me deplorable and malignant facts.

Our visitor paused in his narration, trying to remember exactly the situation presented.

- Then, I decided to confront Marcus so that he could explain the facts. To my surprise, Marcus had disappeared. Since that episode, I have not heard from him, and no one has been able to tell me anything about his whereabouts. I am concerned Mr. Holmes, Marcus has been a commendable employee and I cannot explain what has been reported to me.

Holmes listened attentively to the story. His abstracted expression accompanied the smoke from his pipe. He stood up resolutely and addressed our visitor.

- Well, Mr. Rydeberg, this matter deserves our earliest participation. Tomorrow, together with Dr. Watson, we shall be at your establishment.

With these words, Mr. Rydeberg withdrew with a more composed face.

As the visitor retired, I referred to Holmes my presumption about the case.

- I think it is a simple case, Holmes. The man was caught for previous faults and decided to change town.

- Watson, Watson…you must understand that the most complex cases can be found behind a simple scenario.

In the morning we took the 08:37 train to the nearest town of Mirrortown and then continued from there by carriage.

As we approached Mr. Rydeberg's facilities, we noticed a modest building of dark red bricks in a good state of maintenance. We entered the place and our acquaintance was waiting for us. After comments on the production of the drink, Holmes asked:

- Where was your client's lady cousin and where was Marcus?

After a series of indications Holmes commented:

- I see they were both within 4 feet of each other. Did you notice any change in Marcus as the cousin entered?

Our client took his time to ponder.

- Not really. Marcus was unaffected by the lady's entrance.

- Correct, said Holmes: it would appear that the lady knew Marcus, but Marcus showed no signs of knowing the lady.

Holmes's remark was remarkable to me, but I did not stop at it. Remembering my prudent knowledge, I decided to look through the lens of a microscope that stood near the light of a window.

On seeing me, Mr. Rydeberg said:

- Ah. I was looking at a common deposit formed in the production of wine.

I looked with interest at the lens and said:

- Oh…interesting! I see something like a mixture of "left-hand gloves" and "right-hand gloves".

After hearing my comment, Holmes approached me and anxiously asked for permission to observe the preparation. Looking up, he exclaimed: (See Figure 1)

- Dr. Watson, your involvement in this case is immeasurable!

He looked away from the microscope and stared at Mr. Rydeberg.

- Mr. Rydeberg: What is Marcus' origin?

- He was recommended to us by an orphanage near the train station that brought you here.

- Thank you Mr. Rydeberg. Watson; we must continue our analysis there.

We set off immediately for the orphanage. The road was narrow and, in parts of the route, there was barren vegetation surrounded by rocks. Holmes, for his part, had entered in his typical taciturn mood, when an idea began to obsess him.

We arrived at the orphanage. A neat entrance allowed us access to the main entrance. On the way, we could see several youngsters making cricket moves.

There was no need to wait, for the mere mention of Holmes' presence led us to the office of the headmistress, Mrs. Strepside.

- Mr. Holmes, may I ask on what I owe such a kindly visit to my humble establishment?

- Your work, on the other hand, far from being humble, is commendable. But in this case, our interest is in the details of Marcus' story….

The director's face hardened and her response was slow in coming.

- He is…he is…an excellent young man and a responsible operator in the tasks in his charge.

- Yes, he is. I believe that. That's true. However, I would like you to tell me about his "twin" brother. What became of him?

The headmistress's shock at hearing the word "twin" came on. In my case, the surprise was total.

- Yes, I forgot that I'm dealing with a clever thinker. Her brother Sydney turned out to be irascible from birth. They were like two peas in a pod, but one had a bitter taste while the other was sweet. More than once we heard of his outrages that embarrassed poor Marcus.

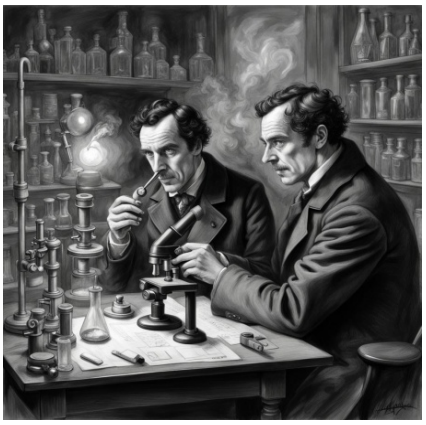

Figure 1. Sherlock Holmes and Dr. Watson in front of the microscope.

On the train back to Baker Street, Holmes pointed out to me:

- We will speak to Inspector Lestrade of Scotland Yard about inviting Sydney to travel to America and start a new life there, under the watchful eye of the local officers. Hopefully, the pain caused to his twin brother will give him pause for reflection.

- What about Marcus now?

- I have already spoken to him and Mr. Rydeberg. I have no doubt that he will continue his life there normally.

So, we closed the case which, in my files, I referred to as "The Racemic Case".

3. Suggestions for Classroom Work

The presentation of the topic enantiomers is done in the first years of medical courses and is usually explained with the characteristics of the functional groups.

The D- and L-glyceraldehyde molecules are the introduction to the explanation of the properties of carbohydrates, centered on D-glucose. The subject is then relegated to the second place and little or nothing is explained about the medical significance of the L- or D-forms or the racemic mixture of a drug.

3.1. Introductory Activity to the Subject Matter: Analysis and Interpretation of the Story

This first activity will consist of reading and later discussing the story, in order to relate the situation to the disciplinary topic, *i.e.*, enantiomers. For this purpose, the teacher can give a theoretical introduction or ask the students to study the topic before attending the class. In the classroom, the teacher will propose a general or group discussion so that students can establish the relationships required. In this respect, the following topics can be considered:

1) In the Sherlock Holmes story presented, in introductory form, Dr. Watson observes crystals that form when making wine and that can be considered "gloves of different hands". Normally, in the production of this beverage, a precipitate of a racemic organic compound, tartaric acid, appears.

2) The observation under the microscope leads Holmes to a conjecture that solves the case, using an analogy. Although we do not know how Holmes processes Watson's comment, we could sketch a possible path followed by the detective to approach the teaching of enantiomers:

"Microscope observation → gloves → twins".

Holmes sees crystals of different orientations, characteristic of a racemic mixture.

3) Holmes, who is an encyclopedia, knows about Pasteur's work. A compound with the same molecular formula can have atoms with different orientations in space. These different shapes have different chemical and physical properties. It is not just a matter of interaction with polarized light. Holmes' mind went further while Watson only observed crystals. The teacher can suggest to the students to look for information about this work, and how Pasteur was able to es-

tablish this characteristic of enantiomers. Microscopic observation of this compound (Figure 2) shows the forms of tartaric acid that trigger Holmes' comments.

4) The situation referred to by Mr. Rydeberg can be explained by two twin brothers: "same formula", but different social behavior. (See Figure 3)

3.2. Application Activity: Previous Knowledge and the Search for Information

At this point, the teacher explores the students' prior knowledge of the disciplinary topic, for which we suggest some possible questions:

- What molecules do they know that have enantiomers?

- Which specific enantiomers (R or S) of certain compounds are used in any medical treatment?

- Which racemic mixtures of specific enantiomers are used in any medical treatment?

- Do you know the case of thalidomide? Explain this case. (See Figure 4)

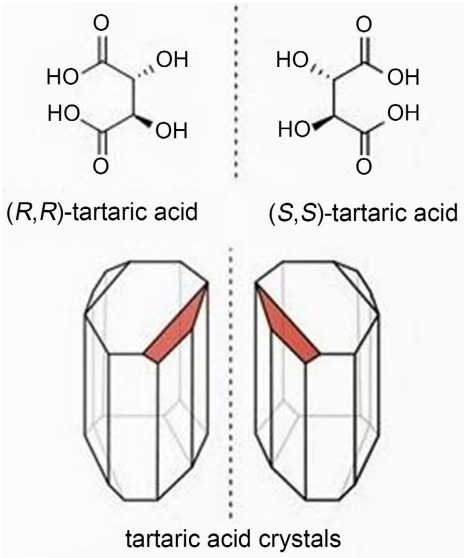

Figure 2. Crystals of tartaric acid formed by its two enantiomers.

Figure 3. Mirror images.

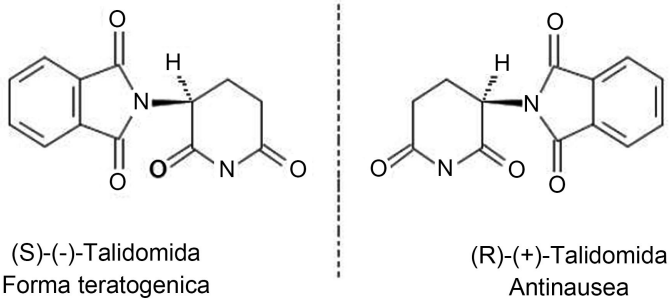

Figure 4. Forms of thalidomide.

The teacher tells the students that they can search the web for information to guide them in their answers. About 10 - 15 minutes later there will be a considerable amount of information, mostly without a teaching context or conceptual framework.

3.3. Correlation Activities: Linking the Story to Discipline-Specific Content

As a start, the teacher can mention the link between the different observations in the story, comparing the "looks" of Holmes and Dr. Watson (Table 1). The facts give rise to the following table of implications.

3.4. Application Activities: Students Are Asked to Research the Most Medically Relevant Compounds with Enantiomers, Their Use, and Their Pharmacological Importance

Based on the information provided by the students, the teacher draws up a table. As an example, Table 2 shows the main medically relevant compounds presenting mirror images or enantiomers. Although this text doesn't aim to provide an introduction to pharmacology, it is necessary to bear in mind that drug action can be either non-specific or specific. Nonspecific drugs are those that do not depend on interaction with a receptor to generate an effect, and the effect depends on their physicochemical characteristics. A case of non-specificity is presented by the ethanol molecule (CH3CH2OH). In Bioenergetics there are examples of non-specificity compounds with "high-energy bonds". In those cases, the characteristic of the action of the compound within the metabolism can be explained by a characteristic of the molecule itself.

In contrast, the action of the compounds in Table 2 depends on binding to another molecule, a receptor; these are drugs with a specific action.

It should be noted that Watson's microscopic observation in the story allows us to distinguish crystals and not molecules of tartaric acid. Each molecule, when interacting with the solvent, generates a crystal opposite to its enantiomer.

At this point, the teacher will discuss with the students examples of many other drugs currently available as racemic mixtures, whose enantiomers are of importance in different aspects of clinical pharmacology. The differences that arise are referred to as stereoselective mechanisms, which may be pharmacoki-

netic or pharmacodynamic and have different pharmaceutical and/or clinical implications.

Table 1. Correlation between Watson's and Holmes' observations and Holmes' inferences.

Observations by Watson and Holmes. Holmes' inferences	Disciplinary Content
Mirrortown	The city refers to a mirror, which will be related at the end of the story to the mirror image of enantiomers.
"Left-hand gloves" and "right-hand gloves"	R and S enantiomers of the compound precipitated in wine (tartaric acid). These molecules are, like hands, non-superimposable mirror images in the plane.
Twin brothers	R and S enantiomers. In many cases, one of the two may be harmful to health (see the Annex)
"Liike two peas in a pod, but one had a bitter taste while the other was sweet."	The racemic mixture, with both enantiomers: seemingly identical, but the subtlety of the spatial configuration of the substituents gives them different properties.
"his actions (Sydney's) that embarrassed poor Marcus"	The racemic mixture that causes an unwanted effect (See the Annex for the case of thalidomide)
Marcus (good brother)	One of the two enantiomers, in this case, the one that has no harmful effect or the one that has a beneficial effect on health,, if we extrapolate it to the medical plane to be taught.
Sydney (irascible brother)	One of the two enantiomers, in this case, the one that has a harmful effect on health, if we extrapolate it to the medical plane to be taught.

Link with enantiomers.

Table 2. Medically relevant compounds presenting enantiomers.

Compound	Enantiomers	Actions and Uses	Pharmacological Importance
Nebivolol	Enantiomers D	β-blockade	Pharmacodynamic Advantages
	Enantiomers L	Vasodilatation	
Labetalol	Isomer R, R	Potent β1-blockade Intrinsic β2-sympathomimetic activity	Hypotensive action, use in hypertensive crises
	Isomer R, S	No activity	
	Isomer S, R	Powerful α1 blocking	
	Isomer S, S	Strong blocking α1	
Carvedilol	Enantiomers R (+)	Blocking α1, antioxidant	Effects on blood pressure and metabolic diseases
	Enantiomers S (−)	Blocking β1, β2, α1	
Propranolol	Enantiomers R (+)	Blocking β	Stereo-selectivity in pharmacokinetics
	Enantiomers S (−)	Blocking β, major τ1/2	
Dobutamina	Enantiomers (−)	Potent α1 agonist β1, β2 agonist	Stereoisomers influence vascular and cardiac responses
	Enantiomers (+)	Powerful α1 antagonist β1, β2 agonist	

More detailed properties of the compounds are presented in the form of an Annex. Students can expand on the compounds based on their future medical interest (Brunton L.L. and Knollmann B.C., 2023) [10].

4. Conclusions

Didactic proposals based on mystery stories can motivate, arouse interest, and facilitate the learning of various topics from different disciplines [3] [5] [11]. Examples include stories related to chemistry and physics [6] [12] [13], biology [2] [14], and applied disciplines such as medicine [4] or different branches of technology. In this sense, the European TEMI (Teaching Enquiry with Mysteries) project, for example, seeks to bring about a change in the way natural sciences, mathematics, and technology are taught [15].

We believe that this new contribution makes it possible to work in the science classroom, in this particular case when applied to pharmacology, using an attractive approach for students that will allow them to develop integrated learning of content, from a basic discipline such as chemistry to an applied discipline such as pharmacology. The teacher is recommended to keep the suspense of the solution of the story in order to maintain the motivation or hypothesization of the student.

Conflicts of Interest

The authors declare no conflicts of interest.

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Annex. Pharmacology of the Enantiomers in Table 2

Nebivolol: Nebivolol was approved for the treatment of hypertension and has potential utility in the treatment of heart failure with reduced ejection fraction. Nebivolol also reduces oxidative stress and may have favorable effects on both carbohydrate and lipid metabolism. These benefits are also observed in the presence of metabolic syndrome, which is often accompanied by hypertension (Ignarro, 2008).

Nebivolol is administered as a racemate containing equal amounts of the D and L enantiomers. The D isomer is the active β-blocking component; the L isomer is responsible for enhancing NO production.

Labetalol: It is a third-generation β-adrenergic receptor antagonist. It has two optical centers, and the clinically used formulation contains equal amounts of all four diastereoisomers.

- The R, R isomer accounts for much of the β-blockade produced by the mixture of isomers. As an $\alpha 1$ antagonist, this isomer is less potent (20%) than the racemic mixture. The R, R isomer has some intrinsic sympathomimetic activity at $\beta 2$-adrenergic receptors; this may contribute to vasodilation.

- The R, S isomer is almost devoid of α- and β-blocking effects.

- The S, R isomer has almost no β-blocking activity, but is approximately five times more potent as an $\alpha 1$-blocker than racemic labetalol.

- The S, S isomer is deprived of β-blocking activity and has a potency similar to that of racemic labetalol as an $\alpha 1$-receptor antagonist.

Labetalol is available in oral form for the treatment of chronic hypertension and as an intravenous form for use in hypertensive emergencies. It has been recommended as a treatment for severe acute hypertension (hypertensive emergency). It can be used in the setting of pregnancy-induced hypertensive crisis, because transfer across the placenta is ineffective due to the low lipid solubility of labetalol, but primarily because it has the strongest evidence of use and safety.

Carvedilol: A third-generation β-receptor antagonist with a unique pharmacological profile. It blocks $\beta 1$, $\beta 2$, and $\alpha 1$ receptors in a similar way to labetalol, but also has antioxidant and anti-inflammatory properties (Dandona *et al.*, 2007). It is another β-blocker that is marketed in a racemic mixture. The S (−) enantiomer is responsible for blocking the $\beta 1$-adrenergic receptor. The R (+) and S (−) enantiomers have almost equivalent $\alpha 1$-receptor blocking activity.

Carvedilol lowers arterial blood pressure by decreasing vascular resistance and maintaining cardiac output while decreasing vascular sympathetic tone (DiNicolantonio *et al.*, 2015; Zepeda *et al.*, 2012). The drug is FDA-approved for use in hypertension, congestive heart failure, and left ventricular dysfunction following myocardial infarction.

Propranolol: A first-generation β-receptor antagonist.

It has the S-(−) enantiomer which is 100 times more active than the R (+) enantiomer.

In the case of propranolol, stereoselectivity is mainly seen in pharmacokinetic

phenomena. The (−) enantiomer of propranolol appears to be eliminated more slowly from the body than the inactive enantiomer. Propranolol clearance may vary with hepatic blood flow and liver disease, and may also change during administration of other drugs that affect hepatic metabolism.

Dobutamine. Dobutamine is the β-adrenergic agonist of choice for the treatment of acute heart failure patients with systolic dysfunction. Dobutamine has relatively well-balanced cardiac and vascular actions: stimulation of cardiac output with less tachycardia than adrenaline and with a concomitant decrease in pulmonary artery wedge pressure. The main hemodynamic effect of dobutamine is an increase in positive inotropic stroke volume, augmented by a small decrease in systemic vascular resistance and thus afterload.

Dobutamine has a center of asymmetry; both enantiomeric forms are present in the clinically used racemate. The (−) isomer of dobutamine is a potent α1-agonist and can cause significant pressure responses. In contrast, (+) dobutamine is a potent α1-receptor antagonist, which can block the effects of (−) dobutamine. Both isomers are full agonists at β-receptors; the (+) isomer is a more potent β-agonist than the (−) isomer, approximately 10-fold.