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SCIENTIFIC INVESTIGATIONS OF THE NOBEL PRIZE WINNER EMIL FISCHER AS A LAUNCHING PAD FOR THE DEVELOPMENT OF BIOCHEMISTRY: A BRIEF OVERVIEW

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Modern biochemistry and molecular biology would be impossible without discoveries in related fields of science. This paper aims to outline briefly the main stages of scientific activity of a Nobel Prize winner 1902 – German chemist Hermann Emil Fischer, one of the leading chemists of all times. Emil Fischer was a brilliant multifaceted scientist who left his mark in organic chemistry, physiology, medicine, gave impetus to the development of biochemistry. His insights into the structures of sugars, enzymes, proteins, and purines have become a launching pad for the further development of biochemistry and molecular biology. His contribution to the natural sciences was immense; some chemical reactions and concepts were named after him. This prominent scientist was honored with a number of awards.

K e y w o r d s: Emil Fischer, Nobel Prize, Biochemistry, phenylhydrazine, purines, sugars, enzymes, proteins, the lock-and-key model, Fischer Projection, peptide bond.

The original Nobel Prizes were established in 1895 in the fields of Physics, Chemistry, Physiology or Medicine, Literature, Peace [1]. In 1968 the Swedish central bank set up The Sveriges Riksbank Prize in Economic Sciences in Memory of Alfred Nobel, which is better known as the Nobel Memorial Prize in Economic Sciences. There is no the Nobel Prize in Biochemistry and Molecular Biology, since these sciences are too young. *"Biochemistry is a young science, having been known under that term only since about 1900. Its origins, however, can be traced much further back; its early history is part of the early history of both physiology and chemistry"* [2]. Molecular biology as a separate field of biochemistry started forming in the 1930's and finally established in the 1950's [3]. However, were Alfred Nobel alive today, he would definitely establish the prize in biochemistry and molecular biology due to the fact that many discoveries in these fields of sciences became sensational and had a great scientific and social significance.

The recognition of pluralistic interpretation of reality in postmodern era forces scientific community to reconsider the entire scientific worldview. Many well-established scientific theories give rise to the new multifaceted branches of knowledge and are quite often altered by them. This leads to the new explanation and understanding of reality [4].

Biochemistry is also chemistry that explores the chemical processes within and/or related to living organisms. Using chemical tools and focusing on the processes at a molecular level, biochemistry seeks to explain and solve the enigma of life. Largely rooted biochemistry, molecular biology is concerned with molecular structures and phenomena that provide storage of hereditary information and mechanisms for its implementation. Thus, biochemistry and molecular biology may be seen as the foundation of the Life Sciences.

Modern biochemistry and molecular biology would have been impossible without discoveries in related fields of science, in particular, the discoveries

Hermann Emil Fischer (1852-1919)

of the famous scientists who have won the Nobel Prizes. This paper aims to outline briefly the main stages of scientific activity of a Nobel Prize winner – German chemist ***Hermann Emil Fischer*** who is known as the "Father of Biochemistry" [5].

Herrmann Emil Fischer is regarded as one of the leading chemists of all times. His insights into the structures of sugars, enzymes, proteins, and purines laid the foundations for modern biochemistry. The second Nobel Prize in Chemistry 1902 was awarded to Emil Fischer "*in recognition of the extraordinary services he has rendered by his work on sugar and purine syntheses*" [6]. His work had a direct relation to biochemistry, as well as his subsequent research. The discovery of hydrazine derivatives was a brilliant solution to the problem of obtaining sugars and other compounds synthetically. Moreover, his method of synthesis of glycosides proved to be important for plant physiology and biochemistry. In his Nobel lecture, Fischer emphasized:

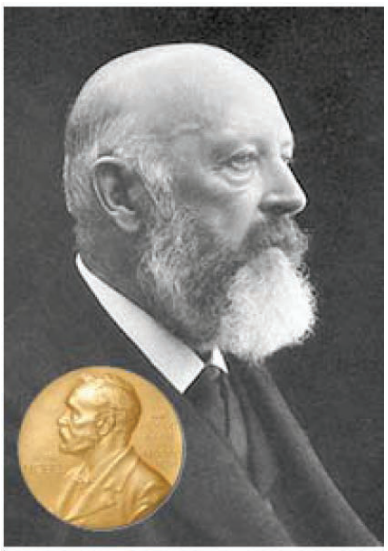
"And so, progressively, the veil behind which Nature has so carefully concealed her secrets is being lifted where the carbohydrates are concerned. Nevertheless, the chemical enigma of Life will not be solved until organic chemistry has mastered another, even more difficult subject, the proteins, in the same way as it has mastered the carbohydrates. It is hence understandable that the organic and physiological chemists are increasingly turning their attention to it and I, too, have been concerned with it for a number of years" [7].

In 1902, Fischer's exploration of protein properties had not yet given the results to be awarded with such a high reward, but later they were evaluated as excellent.

Hermann Emil Fischer was born on October 9, 1852, at Euskirchen, in the Cologne district, Germany, in the family of successful businessman Laurenz Fischer and his wife Julie Fischer. After three years with a private tutor Emil Fischer attended the local school, then he spent two years at school at Wetzlar, and two more at Bonn. In 1869, he passed his final examination with great distinction. Emil loved science, his bright mind wanted to pursue higher studies, but his father wished him to enter the family lumber business. Being quite an unsuccessful businessmen, in 1871 Emil Fischer went to the University of Bonn to study chemistry. He attended the lectures of Kekulé, Engelbach and Zincke, Kundt on physics, Groth on mineralogy [7].

Initially inclined to specialize in physics, he moved to the newly established University of Strasbourg in 1872, along with his cousin Otto Fischer who would later become his research partner. Here Emil met ***Adolf von Baeyer***, an organic chemist who studied dye molecules and later won the Nobel Prize, and finally decided to study chemistry.

Fischer worked on the phthalein dyes. In 1874 he took his PhD at Strasbourg with the thesis on fluorescence and orcin-phthalein. In the same year he was appointed assistant instructor at Strasbourg University where he began his magnificent scientific path. He discovered phenylhydrazine and demonstrated its relationship to hydrazobenzene and to sulphonic acid. Despite the fact that for twelve years Fisher had suffered from the toxic effects of this sub-



Adolf von Baeyer (1835-1917)

stance, he later called phenylhydrazine *"the first and greatest chemical affection"*. This discovery was related to a lot of Fischer's explorations [8].

In 1875 Fischer accompanied von Baeyer to the University of Munich as an assistant. Three years later, in 1878, title of Privatdozent was conferred on him and he was allowed to teach university level courses. In 1879 he was appointed Associate Professor of Analytical Chemistry. During this time he was absorbed by the study of hydrazines.

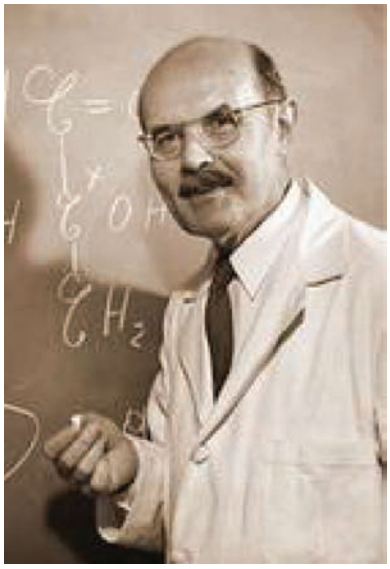
In 1881 he was appointed Professor of Chemistry at the University of Erlangen.

In 1885 he became Professor of Chemistry at the University of Würzburg.

In 1888 Emil Fischer married Agnes Gerlach, daughter of J. von Gerlach, Professor of Anatomy at Erlangen. She died seven years after their marriage in 1895. They had three sons. With the onset of World War I, all Fischer's sons were drafted into the German Army. One of them was killed, another committed suicide. The third son, ***Hermann Otto Laurenz Fischer***, was soon transferred as a staff officer to the chemical warfare unit and survived the war. He became a famous organic chemist and biochemist; was Professor of Biochemistry at the University of California at Berkeley [10].


Ludwig II
von Gottes Gnaden König von Bayern,
Pfalzgraf bey Rhein,
Herzog von Bayern, Franken und in Schwaben z.z.

Fischer's appointment patent from 1885, personally signed by Ludwig II of Bavaria [9]

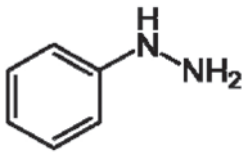


Hermann Otto Laurenz Fischer (1888-1960)

In 1892 Emil Fischer was asked to succeed A. W. Hofmann in the Chair of Chemistry at the University of Berlin. Here he remained until his death in 1919 [7]. Suffering from terminal cancer and deeply depressed over the deaths of two of his three sons in World War I, he took his own life.

Emil Fischer was a brilliant scientist who left his mark in organic chemistry, physiology, medicine, gave impetus to the development of biochemistry. His early significant discovery was the first hydrazine derivative compound – phenylhydrazine. Working in Munich with Otto Fischer, they introduced their theory of the constitution of triphenylmethane dyes and proved it by experiment [11]. Along, Emil Fischer continued working on the hydrazines.

At Erlangen Fischer investigated the active substances of tea, coffee and cocoa, isolating caffeine from tea and coffee and theobromine from cocoa. He demonstrated that caffeine and theobromine, uric acid and guanine, adenine and xanthine have a simi-



Phenylhydrazine formula

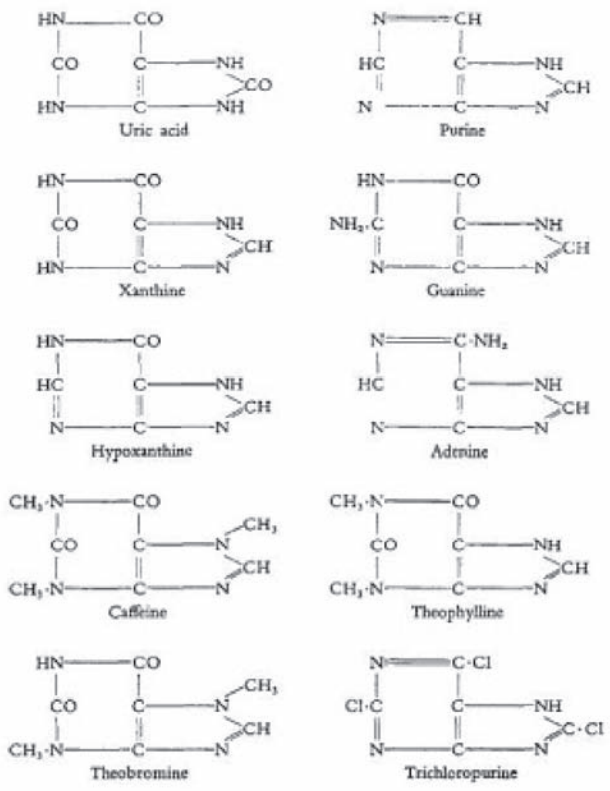
lar structure and can be derived from one another. He came to the conclusion that they belong to one family. The 'mother' substance he called purine in 1884 and synthesized it in 1898 [7]. Emil Fischer stated:

"…the name "purines" is a generic term for a large class of nitrogenous organic compounds, some being certain animal excretions and others the active constituents of important stimulating beverages. The oldest member of the group is known by the rather unattractive name of uric acid and was discovered in this country 126 years ago simultaneously by Scheele and his famous friend Torbern Bergman as a constituent of urinary calculus and urine. To the physician it is familiar as the cause of painful afflictions, e.g. gout. It appeals to zoologists as the main excrement of snakes and as the reserve material of insects. And finally the enlightened farmer knows it to be a valuable constituent of guano...

Rather closely related to uric acid in composition and external characteristics are four other substances occurring in the bodies of animals, xanthine, hypoxanthine, adenine and guanine, the first three of which were discovered in the muscular substance and the last in guano. Thanks to the progress of physiological chemistry we now know that these four substances are important constituents of the cell nucleus and therefore have great biological significance.

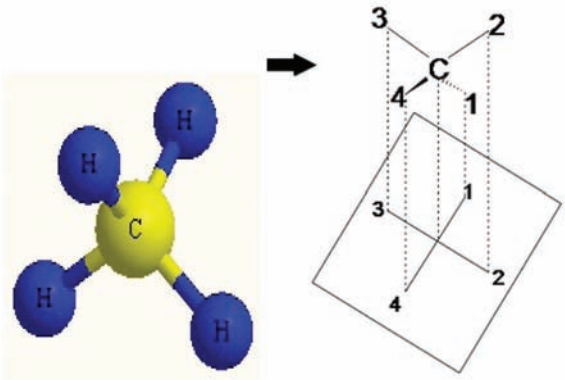
These animal products are joined by three substances from the vegetable kingdom, caffeine, theobromine and theophylline" [7].

Reporting on his work, Fischer mentioned these purines:



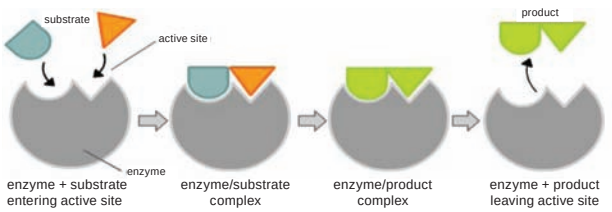
Purines are one of the most widespread classes of organic compounds present in Nature [7]. Adenine and guanine are the building blocks of DNA. The famous scientist synthesized about 130 related compounds, one of which was the first synthetic nucleotide. These studies led to the synthesis of powerful hypnotic drugs derived from barbituric acids (barbiturates) [12].

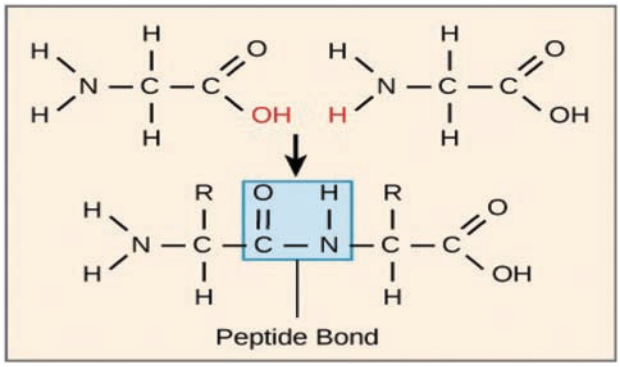
Working on purines, Fisher began his great work on sugars in 1884. Fisher started with exploring glucose trying to figure out the shape of carbon skeleton, as well as the nature, location and spatial positioning of its functional groups. Developing new reagents, methods, procedures, he was successful to interpret his experimental results [13]. Previously discovered phenylhydrazine made it possible to form the phenylhydrazones and the osazones. He established the structural relationship between glucose, fructose and mannose; the stereochemical nature and isomery of the sugars, determined the group of sugars known as hexoses. He devised the Fischer Projection method to represent the three-dimensional structures of molecules on a 2D surface instead of drawing a more detailed 3D structural representation of the molecule. By convention, horizontal lines symbolize bonds projecting from the plane of the paper toward the viewer, while vertical lines symbolize bonds projecting away from the viewer [14]. This method is used to depict all classes of optical isomers [15]:



Investigating sugars, Fischer went deeper into the fermentation caused in sugar by enzymatic action. His pioneering work on organic compounds including purines and sugars led him to the Nobel Prize he won in 1902.

One of the fundamental discoveries in the scope of biochemistry credited to Emil Fischer is the lock-and-key model for the reaction between enzymes and substrates. It suggests that the enzyme and the substrate possess specific geometric shapes that are





complementary to each other and fit into each other. The active site of the enzyme is like a lock and the substrate fits like a key into this lock. This theory *"became a leading concept for the understanding of intermolecular interactions with proteins, and later for the rational design of drugs. With the advent of supramolecular chemistry the idea gained an enormous momentum, as chemists began to synthesize a large variety of host compounds for practically all possible target guest molecules occurring in nature or in the environment"*, though this theory has some limitations and extensions [16].

Fischer's investigations into the chemistry of proteins began 1899. Before synthesizing peptides, he turned to the amino acids as to the building blocks of them. Fischer introduced methods for separation and identification of amino acids in protein hydrolysates; discovered the new cyclic amino acids, L-Proline and L-Hydroxyproline; synthesized ornithine in 1901, serine in 1902, and the sulphur-containing cysteine in 1908; created small chains of amino acids as precursors to protein formation [12, 13, 17]. Obtaining amino acids in an optically-active form, Fischer carried out an investigation on the proteins' syntheses. He was able to recognize how the amino acids are linked together by what are known as peptide bond – the type of bond that would connect them together in chains. He obtained the dipeptides, tripeptides, and polypeptides. Fischer's scientific activity led to a better understanding of the proteins and laid the foundations for the further studies.

Emil Fischer was a versatile chemist. Along with studying purines, sugars, proteins, he contributed to other areas: dyes, tanning chemicals, chemical substances in the lichens, indoles, barbiturates. In 1903 he synthesized the first barbiturate – barbituric acid that contributed to the development of affordable sedatives for insomnia and anxiety [18].

Emil Fischer in laboratoty [9]

Fischer's scientific activity on purines, sugars, proteins has become a launching pad for the further development of biochemistry and molecular biology. "Fischer published more than 600 scientific articles which have been collected in eight volumes under the following titles:

1. Triphenylmethane dyes.
2. Hydrazine and indoles.
3. Purines.
4 & 5. Carbohydrates and enzymes.
6 & 7. Amino acids, polypeptides and proteins.
8. Dye stuff.

A large number, around 330, of doctoral and postdoctoral co-workers from many countries worked with Fischer. Many of them carried forward his scientific legacy and contributed significantly to organic chemistry, biochemistry, and medicinal chemistry research in academic institutions and industry, and several of them won Nobel Prizes" [13].

Fischer's contribution to the field of natural sciences was immense; some chemical reactions and concepts were named after him: Fischer indole synthesis; Fischer projection; Fischer oxazole synthesis; Fischer peptide synthesis; Fischer phenylhydrazine and oxazone reaction; Fischer reduction; Fischer–Speier esterification; Fischer glycosidation [19].

This prominent scientist was honored with a number of awards.

In 1890 for an outstandingly important recent discovery in chemistry Fischer received *Davy Medal awarded by the Royal Society of London*. In 1902 he won *the Nobel Prize in Chemistry.* The honors received by Fischer include *the Prussian Order of Merit and the Maximilian Order for Arts & Sciences.* In 1907 he was honored with *the Faraday Medal of the English Chemical Society* and with *honorary membership in the American Chemical society* [20]. In 1909 for his work on sugar and protein chemistry, he received *Helmholtz Medal* – an award to scholars for excellence in the areas of natural science, technology, medicine, epistemology, humanities and social sciences. In 1913 he was honored by *Elliot Cresson Medal* – the highest award given by the Franklin Institute until 1998. *When Fischer died, the Emil Fischer Memorial Medal was instituted by the German Chemical Society.* In 1968 Hermann Emil Fischer was honored again as one of the greatest scientists in human history: his biography was included in the *World Who's Who in Science* [21]. *The Fischer lunar crater* was named in his honor and in honor of the other outstanding German organic chemist Hans Fischer who won the 1930 Nobel Prize [22].

Fischer lunar crater

In 2008 in order to honor active carbohydrate scientists distinguished with contributions of excellence, European Carbohydrate Organization (ECO) established *the Emil Fischer Carbohydrate Award* [23]. This award for 2017 has been awarded to *Prof. Carlo Unverzagt* of the University of Bayreuth, Germany, in recognition of his accomplishments in the chemical and enzymatic synthesis of N-glycans and glycoproteins [24].

НАУКОВІ ДОСЛІДЖЕННЯ НОБЕЛІВСЬКОГО ЛАУРЕАТА ЕМІЛЯ ФІШЕРА ЯК СТАРТОВИЙ МАЙДАНЧИК ДЛЯ РОЗВИТКУ БІОХІМІЇ: КОРОТКИЙ ОГЛЯД

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Сучасна біохімія і молекулярна біологія були б неможливі без відкриттів в суміжних галузях науки. У цій статті представлено короткий огляд основних етапів наукової діяльності лауреата Нобелівської премії 1902 року в галузі хімії – німецького хіміка Германа Еміля Фішера, одного з провідних хіміків всіх часів. Еміль Фішер був блискучим багатогранним вченим, який залишив свій слід в органічній хімії, фізіології, медицині, дав поштовх розвитку біохімії. Його глибоке проникнення в структуру цукрів, ензимів, протеїнів і пуринів стало відправною точкою для подальшого розвитку біохімії і молекулярної біології. Його внесок в природничі науки був величезним; деякі хімічні реакції та концепції були названі на його честь. Цей видатний вчений був удостоєний низки нагород найвищого гатунку, включаючи й одну з перших Нобелівських премій.

Ключові слова: Еміль Фішер, Нобелівська премія, біохімія, фенілгідразин, пурини, цукри, ензими, протеїни, модель «замок - ключ», проекція Фішера, пептидний зв'язок.

НАУЧНЫЕ ИССЛЕДОВАНИЯ НОБЕЛЕВСКОГО ЛАУРЕАТА ЭМИЛЯ ФИШЕРА КАК СТАРТОВАЯ ПЛОЩАДКА ДЛЯ РАЗВИТИЯ БИОХИМИИ: КРАТКИЙ ОБЗОР

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Современная биохимия и молекулярная биология были бы невозможны без открытий в смежных областях науки. В этой статье представлен краткий обзор основных этапов научной деятельности лауреата Нобелевской премии 1902 года в области химии - немецкого химика Германа Эмиля Фишера, одного из ведущих химиков всех времен. Эмиль Фишер был блестящим многогранным ученым, который оставил свой след в органической химии, физиологии, медицине, дал толчок развитию биохимии. Его глубокое проникновение в структуру сахаров, энзимов, протеинов и пуринов стало отправной точкой для дальнейшего развития биохимии и молекулярной биологии. Его вклад в естественные науки был огромным; некоторые химические реакции и концепции были названы в его честь. Этот выдающийся ученый был удостоен множества престижных наград, включая Нобелевскую премию.

Ключевые слова: Эмиль Фишер, Нобелевская премия, биохимия, фенилгидразин, пурины, сахара, энзимы, протеины, модель «замок – ключ», проекция Фишера, пептидная связь.

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