Hermann Emil Fischer: Life and Achievements

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Emil Fischer, considered as one of the greatest chemists of all times, carried out much of the fundamental work on purines, sugars, proteins, stereochemistry and several other areas of chemistry during the late nineteenth and early twentieth century. Because most of these are biological molecules, he is known as the 'Father of Biochemistry'. His achievements in chemical synthesis and analytical skills were much ahead of his times. He was the second to get the Nobel Prize in Chemistry in 1902.

Introduction

Carbohydrates, proteins, fats, and nucleic acids are the four major chemical constituents of living organisms. These four classes of organic compounds are the main players in the emergence and existence of life. Extensive pioneering contributions to the development of all these areas of organic chemistry and biochemistry were made by Emil Fischer through his more than four decades of brilliant research work starting from the early 1870s. His uncanny skills in analytical and synthetic work, his extraordinary understanding of the enormous amount of experimental results and their correct interpretation laid a solid foundation for the chemistry of these biologically important molecules. Though his work essentially constituted analytical and synthetic organic chemistry, its reach extended to other areas, particularly stereochemistry, biochemistry, physiology and medicine. As scientific administrator, Fischer established scientific institutions, shaped science education, encouraged development of other branches of science, helped industrial growth and applied science to overcome resource shortfall in Germany during World War I. He is considered as one of the greatest or perhaps the greatest of organic chemists of all time.

Keywords
Purines, sugars, proteins, phenylhydrazine, Fischer, Nobel Prize, World War I.

Personal Life and Early Education

Emil Fischer was born on 9th October, 1852, at Euskirchen in Cologne district (then a part of the Prussian Empire) of Germany. His father, Laurenz Fischer, was a successful business man and was running dye making and brewery units and a profitable lumber business. His mother's name was Julie Fischer. Emil had five older sisters. Both his father and mother were conscientious individuals and had considerable influence on Emil. His father's brother and his family with wife, five sons and a daughter lived next door. Emil spent time with his cousins, one of whom, Otto, later studied chemistry with him. Emil had a happy boyhood.

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Emil studied initially under a private tutor for three years in a private school started by his father and then at Höhere Bürgerschule (Higher Public School) at Euskirchen, after which he went to Gymnasium (high school) at Wetzler for two years. He studied for two more years in the Gymnasium at Bonn. He was very good in his studies and passed with distinction from high school in 1869. Emil had great interest to continue his studies. But his father wanted him to take up the family business. To equip himself for this Emil worked as an apprentice under his brother-in-law who ran lumber business. Emil joined his father in business and assisted him in solving chemistry-related problems in brewing and dye making. Bur Emil's interest to pursue further studies did not diminish, and the young boy was allowed to fulfil his desire. He had great interest in studying physics and mathematics and joined the University of Bonn in 1871, where chemistry was taught by great masters like Kekule[1], Engelbach and Zincke, physics by Kundt and mineralogy by Groth. Though he was impressed by Kekule's teaching, he moved in1872, along with his cousin Otto Fischer, to the University of Strasburg, which was newly reconstituted that year under the Prussian Empire. (In 1918 Strasburg was returned to France. It is presently the biggest university in that country). When Emil and Otto came there they had planned to study Bunsen method of analysis under Professor Rose. However, they came under the influence of the famous organic chemist Adolf von Baeyer and joined him to do

[1] See *Resonance*, Vol.6, No.5, 2001.

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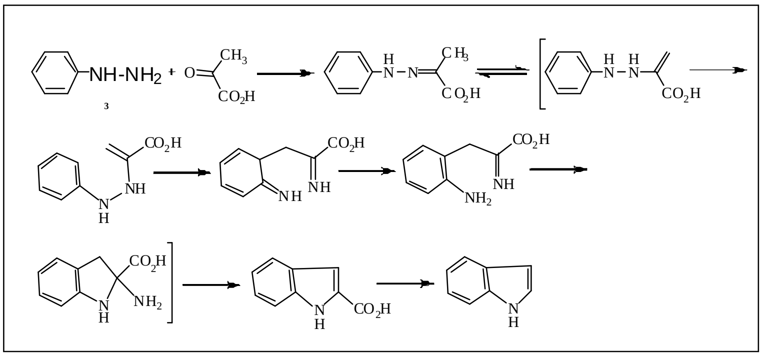
research. Under Baeyer's guidance they worked on phthalein dyes. Emil Fischer studied the chemistry of fluorescein and orcin-phthalein, and obtained Dr. Phil. degree in 1874, and started his long, brilliant academic career in the same year. In 1888, Emil Fischer married Agnes Gerlach, daughter of Joseph von Gerlach who was professor of anatomy at Erlangen University. The couple had three sons. Unfortunately, Agnes did not live much longer and passed away in 1895.

It seems that Fischer suffered from frequent bouts of gastritis from his younger days, which even affected his academic career now and then. Once he had to take a break for a year, while in Erlangen, and forgo an attractive offer to take the Chair of Chemistry at the Swiss Federal Institute of Technology (ETH) at Zurich.

Academic Positions

Soon after obtaining the doctorate degree Fisher started his long academic career in 1874. He was appointed as assistant instructor at Strasburg University. During this period he serendipitously discovered phenylhydrazine, which later became one of the key reagents in his work on the determination of structures of sugars and in the synthesis of heterocyclic compounds (e.g., Fischer indole synthesis, *Scheme* 1).

In 1875 Baeyer went to the University of Munich as successor to Justus von Liebig; Emil and his cousin Otto followed him. Emil Fischer secured a job of assistant there in the organic chemistry



Scheme 1. Fischer indole synthesis.

department. In 1878 he qualified himself to be a faculty member (habilitiert) at the university by submitting a thesis on his phenylhydrazine work and in 1879 was appointed as Privatdezent or Extraordinariat (similar to Associate Professor) for analytical chemistry in the place of Volhard, who moved to Erlangen. In the same year he was offered the Chair of Chemistry at Aachen, but he did not accept it because he considered that the department was not of his expected standards. In 1881, Fischer went to Erlangen as professor, again in the place of Volhard. Two years later, he rejected a lucrative offer from the industrial giant BASF as the director of research, because his first love was academics. However, he was always helpful to industries and supported them in all possible ways throughout his life. After working for seven years in Erlangen, Fischer accepted professorship at Würzburg and established a new department of chemistry. Finally, he moved to the University of Berlin to succeed the famous organic chemist, A W Hofmann. He was invited to this position in preference to senior and well- known chemists, Kekule and Baeyer. The Berlin Government met every request he made for developing the department while accepting the offer. Fischer remained there for twenty years until his death on the 15th of July, 1919.

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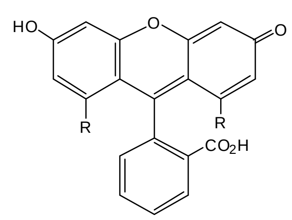
Fischer had an extraordinary memory which served him in good measure to deliver his well-prepared lectures with great effect. He proved, during his entire academic career, to be a magnificent researcher, a great academic administrator and an excellent teacher.

Scientific Achievements

The Beginning – Dyes and Phenylhydrazine

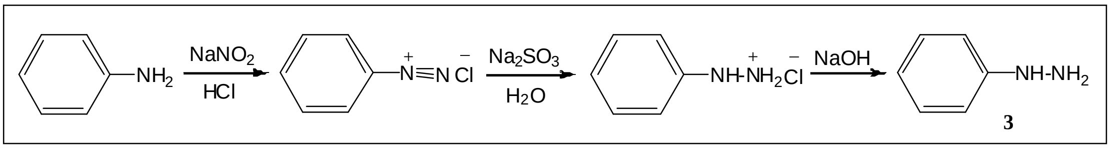
While he was in Strasburg, Fischer worked on triphenylmethane dyes (*Figure* 1), fluorescein (**1**) and orcin-phthalein (**2**). His cousin Otto also worked on similar dyes.

Figure 1.



1: R = OH
2: R = CH_3

His significant discovery here was phenylhydrazine (**3**), which was prepared serendipitously (*Scheme* 2). He continued this work when he went to Munich. He and his cousin Otto together proposed a new theory of the constitution of triphenyl-methane



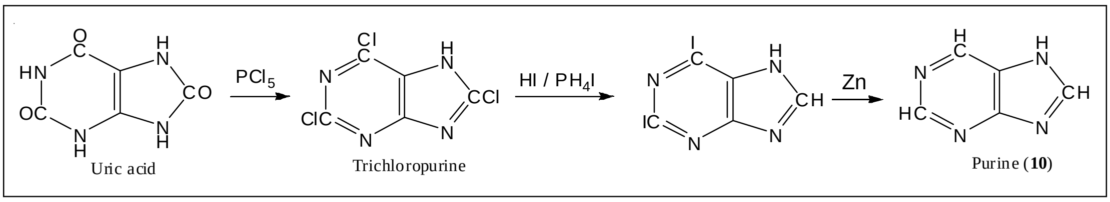
Scheme 2. Preparation of phenylhydrazine.

dyes and proved it experimentally. He worked on the properties and reactions of phenylhydrazine.

Work on Purines – The Chemicals in Coffee, Cocoa, Birds' Excreta, and Cell Nucleus

At Erlangen, Fischer started work on the active principles of coffee, tea and cocoa. He isolated caffeine (**4**) from the first two and theobromine (**5**) from cocoa, and determined their structures by degradation and synthesis. He showed that uric acid (**6**) and guanine (**7**) isolated from excreta of many species of birds and animals are structurally related to caffeine and theobromine as well as adenine (**8**) and xanthine (**9**) isolated from vegetable sources. Starting from uric acid (**6**), Fischer synthesised every one of these related naturally occurring compounds and many new ones as well. As an example, the synthesis of purine from uric acid is given in *Scheme* 3. He demonstrated that all of them are derivatives of a basic fused two-ring nitrogen heterocyclic structure **10**; he called it purine (Greek: *pyre* = burning; Latin: *purus* = fire; Latin: *urina* = urine) and its derivatives prines. Fischer knew 146 natural and synthetic purines in 1902. Purines are one of the most widespread classes of organic compounds present in Nature. Adenine (**8**) and guanine (**7**) were recognised as cell constituents of living organisms. Elucidation of the structures of purines was an important step towards solving the

Scheme 3. Preparation of purine from uric acid.



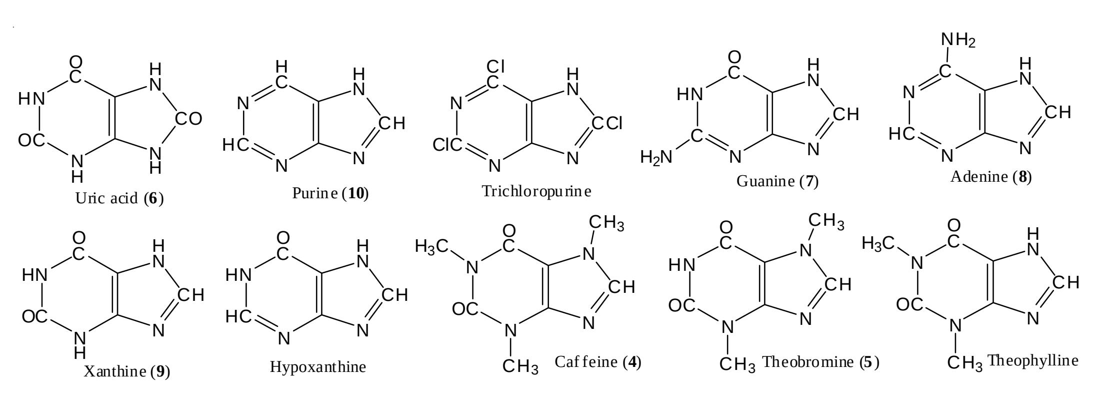


Figure 2. Ten purines mentioned by Fischer in his Nobel Lecture.

constitution of nucleic acids later as nothing was known about the structure of nucleic acids at that time.

Sugars – The Sweet, Short, Long, Three-Dimension Story

Fischer started his work on sugars in 1884 while still working on purines. He chose to study glucose, the most abundant simple sugar, to start with. At that time very little of its chemistry was known, such as its solubility properties, molecular formula, optical activity and the probable presence of the aldehydic function. He had to carry out the daunting task of finding the shape of carbon skeleton, and the nature, location and spatial positioning of its functional groups. As there was no precedence in this area, he had to develop new reagents, new reactions and methodologies, reliable procedures for product analysis, and he had to be able to correctly interpret the results obtained from these experiments. One of the reagents introduced and exploited well was phenylhydrazine (**3**) which he had synthesised at Strasburg. He found that two equivalents of this reagent react with one equivalent of a sugar to give a highly crystalline product which he called osazone. This was very helpful in establishing the structural relationship between simple sugars and in assigning three-dimensional structures if the configuration of one of them is known. For example, Fischer found that glucose, fructose and mannose gave the same osazone, which meant that these three simple sugars differed from one another only at two positions, while the other

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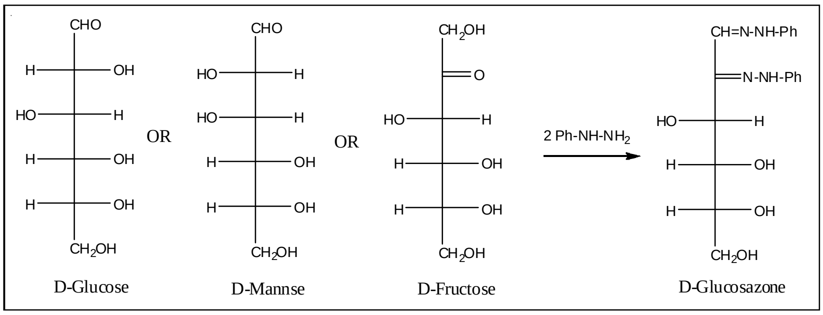
Scheme 4. Single osazone from D-glucose, D-mannose and D-fructose.



four centres should have identical configuration. In fact, Fischer could discover mannose in 1888 by this method (*Scheme* 4).

Fischer used a variety of other reactions such as oxidation, reduction, stepwise degradation, epimerisation, enzyme reactions, and synthesis to derive structural information. He synthesised naturally occurring sugars and new unnatural sugars by lengthening and shortening the chains of the available sugars. For example, he converted tetroses to pentoses, pentoses to hexoses, hexoses to heptoses (Fischer–Kiliani synthesis), and by degradation in the reverse order to get shorter chain sugars. He demonstrated his extraordinary skill in synthesis by preparing, in 1890, glucose, fructose and mannose starting from glycerol. Within three years, during 1891–1894, Fischer had determined the configuration of all the sugars known at that time.

[2] See *Resonance*, Vol.12, No.5, pp.21–30, 2007.

Fischer applied the tetrahedral structural theory of van't Hoff[2] and Le Bel, which was proposed a few years earlier, to substantiate the isomerism of sugars and to correctly predict the possible number of their isomeric structures. To draw three-dimensional structures of these stereoismers on two dimensional surfaces like paper, Fischer started, in 1891, using line drawings, which are

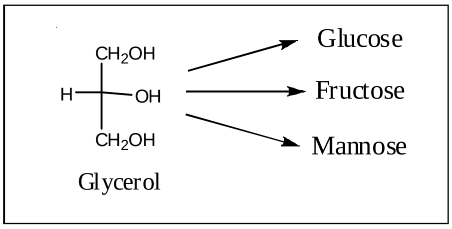


Figure 3. Conversion of glycerol to hexoses.

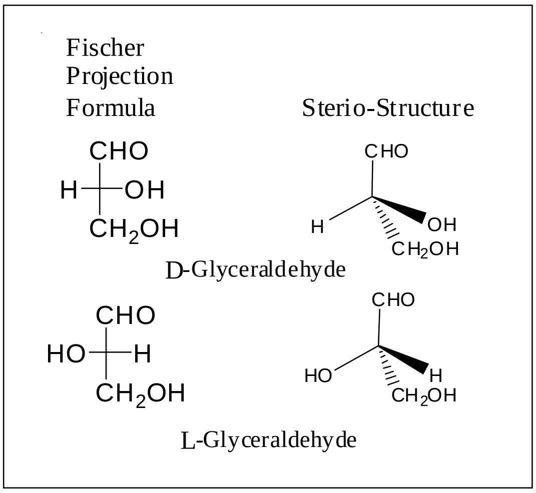


Figure 4. Fischer projections and the wedge structures of glyceraldehydes.

now called 'Fischer projection formulae' (*Figure* 4; see also *Scheme* 4). That is one method we now use to write all classes of optical isomers.

The Lock-and-Key Principle of Enzyme Hydrolysis

In 1894 Fischer discovered that α-methylglucoside and β-methylglucoside, which he had prepared by methylation of glucose, exhibit perfect specificity to enzymes in hydrolysis. He found the α-isomer being hydrolyzed by invertin extracted from yeast and, in contrast, the β-isomer being hydrolyzed by emulsin obtained from almonds, and to his surprise no hydrolysis occurred when the enzymes were interchanged. Fischer's brilliant intellect readily recognized the specificity of enzyme action and its significance in biochemical reactions. He explained the process by comparing it to a lock being opened with a specific key only. He called it the lock-and-key principle model of enzyme hydrolysis, a fundamental discovery in biochemical processes. He studied many natural glycosides also.

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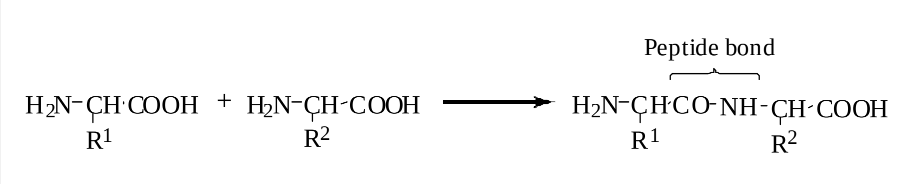
Studies on Proteins, the Workhorses of Life

By 1899 Fischer got interested in the study of proteins and within ten years, i.e., by 1908, he had made several discoveries concerning their properties, reactions, analysis and synthesis. He devel-



Scheme 5. Formation of peptide bond.

oped efficient methods for separation and identification of individual amino acids in protein hydrolysates, discovered the new cyclic amino acids, proline and hydroxyproline, and carried out the hydrolysis and analysis of the milk protein casein in 1901. In the process he recognized how the amino acids are linked together in proteins and peptides, and called the linkage 'peptide bond' (*Scheme* 5).

Armed with this knowledge, Fischer started work on synthesis of peptides. For this purpose he developed appropriate methods to link amino acids in desired order, and prepared dipeptides, tripeptides and higher peptides up to octadecapeptide. He showed that the octadecapeptide behaved like natural proteins in many of its properties. It was not enough for him to use the amino acids isolated from natural proteins, but he synthesized several natural and unnatural amino acids and used them for synthesis of peptides.

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Fischer developed methods for esterification of amino acids needed for peptide synthesis and introduced in 1902 the process of fractional distillation under low pressure to purify these esters at lower temperatures. This eliminated or minimized the decomposition of esters that occurred when they were distilled at high temperatures under normal pressure.

No Full Stop, Only Commas – Other Areas of Research

Fischer did not restrict his work just to purines, sugars and proteins, though the work in these areas by itself required great effort and many resources. He also contributed to other areas such as tanning chemicals, dyes, analysis of lichens collected during his hikes in the Black Forest, the soporific drugs barbiturates (he was the first to synthesize them), indoles (Fischer indole synthesis; see *Scheme* 1) and other heterocycles, rearrangement reactions (Fischer–Hepp reaction and acyl rearrangement), esterification studies, experimental verification of tetrahedral asymmetry at carbon, several analytical procedures and many others. Fischer's work on configurational structures of sugars and amino acids became the solid evidence for van't Hoff and Le Bel's theory of tetrahedral carbon and stereochemistry took deep root. Later in his career Fischer started working on another class of biological molecules, the fats.

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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 stuffs

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.

Honours, Accolades and Awards

The expansive seminal knowledge that Fischer created in the three most important classes of biomolecules, namely, purines (in nucleic acids), carbohydrates and proteins, and to some extent fats as well, provided tremendous impetus in stressing the importance of expanding studies in these areas and on the chemistry of biological systems in general. Because of these fundamental contributions Fischer is considered as 'Father of Biochemistry'.

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The immense influence Fischer had on higher education, scientific research and industrial development in Germany earned him the nickname, "the secret prince of chemists". Carl Dietrich Harries, (a PhD student of Baeyer and an assistant of A W Hofmann at Berlin and later Professor of Organic Chemistry at Kiel University), who worked alongside Fischer in Munich and Berlin, described Fischer thus: "Emil Fischer represents a symbol of Germany's greatness".

A number of streets and schools are named after Emil Fischer.

The Gesellschaft Deutcher Chemiker (The Society of German Chemists) has instituted 'The Emil Fischer Medal' to honour scientists for extraordinary credits in organic chemistry.

Many honours and awards came naturally the way of Fischer, but only a few are listed here. He was awarded Davy Medal in 1890. He received Nobel Prize in Chemistry 1902 and became the second laureate after van't Hoff, but the first organic chemist to be honoured even before his mentor Adolf von Baeyer who got it three years later in 1905. In 1909 Fischer was awarded the Helmholtz Medal for his work on sugar and protein chemistry. He was honoured with the Prussian Order of Merit and Maximilian Order of Arts and Sciences in1913.

In 1900 the Kaiser Wilhelm Institute for Chemistry was planned and built at Berlin under the supervision of Fischer. The institute attracted such great chemists as Otto Diels, Hans Fischer, Otto Warburg and Adolf Windaus, all of whom won Nobel Prizes later.

He was conferred with honorary doctorates of several universities including those of Manchester, Cambridge (England) and Brussels.

Institution Builder and Administrator

Fischer, because of his extraordinary research achievements, had become a highly influential scientist, much respected by scientists, academicians and people in the ruling class. He was a good administrator and a great builder of institutions. He convinced the government of the need to establish a chemical institute devoted to high quality research. Thus in 1900 the Kaiser Wilhelm Institute for Chemistry was planned and built at Berlin under the supervision of Fischer. The institute attracted such great chemists as Otto Diels, Hans Fischer, Otto Warburg and Adolf Windaus, all of whom won Nobel Prizes later. As director of the University of Berlin laboratories, Fischer started a radiochemistry laboratory where Otto Hahn and Lise Meitner worked on uranium fission, which eventually resulted in the making of the atom bomb and producing nuclear energy. Fischer established the Kaiser Wilhelm Society for the Advancement of Sciences, the Institute of Coal Research in Mülheim–Ruhr and after World War I established the German Society for the Advancement of Chemical Instruction. He played an active role in founding the Kaiser Wilhelm Institutes in 1911, which have been renamed as Max Planck Institutes after World War II.

Fischer started a radiochemistry laboratory where Otto Hahn and Lise Meitner worked on uranium fission.

The British blocked the supply of many vital chemicals to Germany during World War I. The shortfall had to be made up from the available resources. Fischer assumed the responsibility to work out methods to produce chemicals in short supply. For example, he helped to develop methods for making potassium nitrate, nitric acid, camphor and sulphur, all of which were needed to make explosives, despite being a pacifist (see his remarks below).

The Dark Shadow of War and Final Years

World War I brought terrible personal tragedy to Fischer. He lost his two younger sons – one was killed in combat and the other killed himself as he could not bear the military training. The eldest son survived (*Box* 1). The sorrowful events greatly affected Fischer's health, which was already delicate due to frequent attacks of gastritis from younger years. He suffered from

Box 1.

The eldest son, Hermann Otto Laurenz Fischer, survived WWI, obtained his PhD from Berlin University and pursued an academic career in biochemistry. Because his wife was of Jewish descent, he migrated to England during WWII. He moved to USA in 1948 and became professor of biochemistry at the University of California, Berkeley. He gave away all the scientific articles, writings, letters, books and other collections of his father to UC, Berkeley, which form the Emil Fischer Library there.

cancer, late in his life, probably caused by handling phenylhydrazine for a long time in his life. All this seems to have made him go into some depression.

War left a deep, devastating impression on Fischer's mind. He was well aware how science is abused in conducting war. Towards the end of WWI in 1917 he wrote to a friend, "Modern warfare in every respect is so horrifying, that scientific people will only regret that it draws its means from the progress of the sciences. I hope that the present war will teach the peoples of Europe a lasting lesson and bring the friends of peace to power. Otherwise the present ruling class will really deserve to be swept away by socialism".

It is ironical that socialism did sweep away the then ruling class soon after WWI, but a more destructive WWI followed not long after. However no lessons are learnt. Scientists are helpless or willing partners in abusing science for war.

Suggested Reading

[1] *Nobel Lectures, Chemistry 1901–1921*, Elsevier, Amsterdam, 1966.
[2] B Helferich, in *Great Chemists*, E Farber (Ed.), 1961.
[3] F W Lichtenthaler, *Eur. J. Org. Chem*., Vol.24, pp.4095–4122, 2002.
[4] F A Carroll, *J. Chem. Educ*., Vol.56, No.2, p.107–109, 1979.

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