EMIL FISCHER'S SAMPLE COLLECTION

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Much has been written about Hermann Emil Fischer's life and work (1-15). His investigations into substances derived from living organisms have influenced generations of chemists. His work led to an understanding of the molecular structures of many biologically important substances, provided numerous methods and laboratory techniques in synthetic organic chemistry, and laid the foundations of the field of biochemistry. His legacy touches every student and practitioner of organic chemistry and biochemistry.

His physical legacy—the actual collection of substances he prepared during his career—has received much less attention. The collection is housed in the Chemistry section of the Deutsches Museum in Munich. This location is particularly fitting because Fischer first attained his professorship less than three kilometers away at the University of Munich. Starting at the nascent Fischer lab, however, the collection would travel through six cities in four countries on two continents before arriving at the Deutsches Museum—a journey of several thousand miles spanning some 115 years.

The collection contains samples that represent work from all stages of Fischer's 45-year career. It is a tangible reminder of the remarkable scope of his work and the importance of the contributions he made in each of the areas of research that he pursued. As of this writing, the samples reside in two large crates and await formal cataloguing by the Deutsches Museum. A brief overview of Fischer's research will provide a sense of the content of the collection and the importance of the work it represents.

The Growth and Significance of the Collection

Conceptually, at least, the compound collection had its origin at the University of Strasbourg, where Fischer earned his doctorate in 1874 under Adolf von Baeyer (16). Continuing to work in von Baeyer's lab after obtaining his degree, Fischer investigated triarylmethane dyes and deduced the structure of phenylhydrazine (17, 18), which figured so prominently in his later work. He proposed the name hydrazine for the saturated nitrogen-nitrogen functional group (17).

In 1875 Fischer moved with von Baeyer to the University of Munich and continued studying organic dyes (19). By 1879 he had risen to the position of Associate Professor of Analytical Chemistry and had his own laboratory (16). Joined by his cousin Otto Fischer in 1876, he continued his work on organic hydrazines and, together with Otto, synthesized the dye pararosaniline from triphenylmethane (20). They then demonstrated that the other dyes in the rosaniline class, which at the time were depicted with a different structure, are actually congeners of triphenylmethane as well (21, 22). The Deutsches Museum has samples of phenylhydrazine and triphenylmethane that represent work from these early years.

The Emil Fischer lab moved in 1882 when Fischer took the position of Professor of Chemistry at the University of Erlangen. It was at Erlangen that Fischer first turned his attention to substances isolated from natural sources, the focus that would define his life's work, and the collection began to grow with new classes of compounds. Fischer showed that uric acid, xanthine, hypoxanthine, adenine, guanine, caffeine, theobromine, and theophylline, though derived from various plant and animal sources, all share a common chemical framework (23, 24). He called the framework "purine" (16, 24), a contraction of the Latin words "purum" and "uricum [acidum]" (8) and thus gave name to a class of compounds of great commercial importance; the immense biological significance of purines as components of nucleic acids, cofactors in metabolic processes, and components of signaling pathways would be recognized much later.

While at Erlangen Fischer also continued work with phenylhydrazine. After investigating its reactions with aldehydes and ketones (25) he discovered that phenylhydrazine reacts with sugars to form highly crystalline derivatives that were easily isolated (26). He called these derivatives osazones (8) and this discovery laid the foundation for his most famous work to come. In separate research he found that phenylhydrazine reacts with ketones to form the indole ring system and elucidated the indole synthesis that bears his name (27, 28).

***Figure 1**. A sample of synthetic glucose from the Emil Fischer compound collection. Copyright Deutsches Museum, Munich, Archive 67265.*

The growing compound collection moved with the Fischer lab to the University of Würzburg when Fischer accepted the position of Professor of Chemistry in 1885 (29). At Würzburg Fischer focused his research on the sugars and produced the work for which he is best known. In 1888 Fischer reported the structure of mannose, a stereoisomer of glucose, which he obtained by oxidizing mannitol (30). By 1890 he had completed the formal syntheses of glucose, fructose, and mannose from glycerol (31, 32) and proposed a nomenclature to designate sugars—the "oses"—having different numbers of carbon atoms (33).

The theory of the tetrahedral atom, its implications for stereoisomerism, and its apparent relationship to optical activity had been put forward by van't Hoff (34) and Le Bel (35) in 1874 (36, 37). Van't Hoff further proposed that there would be 16 stereoisomeric aldohexoses and Fischer undertook to apply the theory to explain the differences between the isomeric sugars (38-40). Through logical application of the theory, Fischer determined the relative stereochemistry of all of the sugars known as of 1894, using D-glucose as a reference (7, 41-43). The diagrams that he developed to display and compare the stereoisomers of sugars are known to all organic chemists as "Fischer Projections" (41, 44). With no way of knowing the absolute stereochemistry of any atom, Fischer adopted the convention of putting the 2-hydroxyl group of D-glucose to the right in the projections (41, 42, 44, 45). With the establishment of this convention the collection became an invaluable source of reference compounds for anyone working in carbohydrate chemistry.

In 1892 Fischer became Chairman of Chemistry at the University of Berlin, succeeding A. W. von Hofmann, and his lab moved yet again. Fischer continued his work on sugars throughout the rest of his career (7, 46, 47); the presence of various synthetic sugars in the collection would attest to this. His modification and use of the Kiliani synthesis of sugars is one of the earliest and most important instances of stereoselective synthesis (1). He showed the relationship between pentoses, hexoses, and heptoses by degradation and synthesis (48). The exquisite selectivity shown by enzymes for stereoisomeric sugars and glucosides led him to draw the analogy of a lock and key to describe the complementarity between an enzyme and its substrate (49, 50). This is a concept that has informed enzymology and receptor research ever since (51).

In Berlin Fischer began his work on amino acids and peptones, the digestive products of proteins, and compounds from another major area of biological chemistry started entering the collection. From the hydrolysis of a variety of protein products he identified two new cyclic amino acids: α-pyrrolidinecarboxylic acid (52), which he later named proline (53), and hydroxy α-pyrrolidinecarboxylic acid (54).

By analogy with the saccharides, he coined the word peptide (55, 56) to describe chains of amino acids of discrete lengths to differentiate them from peptones, which are mixtures of amino acids and peptides of varying length. He explored methods of synthesizing peptides, founding a rich field of research (57-59). He prepared dipeptides, tripeptides, and numerous oligopeptides, the largest of which contained 18 amino acids (60). The preparation of the latter would be a respectable accomplishment even with today's techniques. The thermal instability of the amino acid esters used in his peptide syntheses led Fischer to develop the technique of vacuum fractional distillation, which allowed the separation of the compounds at lower temperatures (61).

Fischer's tenure in Berlin resulted in additional research in diverse areas, including the perfection of acid-catalyzed esterification (62), the synthesis of oxazoles (63), the synthesis of glucosides (64, 65), the synthesis of barbiturates (66, 67), and the synthesis of glycerides along with studies of their properties (68, 69). Later in his tenure at Berlin he studied the properties and syntheses of tannins and depsides (70-73). Some of the work on the depsides was undertaken with his son (74), Hermann Otto Laurenz Fischer, who joined the lab after earning his doctorate under Ludwig Knorr from the University of Jena (73, 75).

Fischer continued his work with the purines only briefly in Berlin (73) but he developed syntheses for numerous purine analogs, including adenine (Figure 2) and guanine (76), uric acid, and caffeine (77). By the time of his address to the Nobel Committee in 1902, Fischer knew of 146 natural and synthetic purines (24), a number of which are represented in the collection.

***Figure 2**. A sample of synthetic adenine from the Emil Fischer compound collection. Copyright Deutsches Museum, Munich, Archive 67267.*

The Collection After Fischer

Upon Emil Fischer's death in 1919, the stewardship of the sample collection fell to his son Hermann, who became an Assistant Professor in the Chemical Institute at the University of Berlin in 1924 (73). His distinguished career included ground-breaking work in the study of trioses, inositols, and glycerides (73, 75, 78). In addition to the compound collection, Hermann Fischer now looked after his father's library (3, 73 ,78) of some 4000 historic chemistry books, his laboratory notebooks and manuscripts, and a handsome, carved oaken laboratory stool that his father had inherited from A. W. von Hofmann in Berlin (3, 73, 78).

With the political climate in Germany deteriorating in the early 1930s, Hermann Fischer chose to accept a position at the University of Basel in Switzerland in 1932 and Emil Fischer's entire sample collection, his library, and laboratory stool began their international journey (73, 78).

As Europe moved towards war Hermann Fischer did not want his sons to serve in the army for a cause in which they and he did not believe (73). In 1937 Hermann Fischer accepted a position at the Banting Institute of the University of Toronto (73), and the Fischer lab moved once again, now crossing the Atlantic to North America.

In 1948 Hermann Fischer accepted the invitation of Wendell M. Stanley to join the Biochemistry and Virus Laboratory that he was organizing at the University of California at Berkeley, and the laboratory with its sample collection, library, and laboratory chair moved yet again (73, 78). At the official opening of the laboratory in 1952, Hermann Fischer donated his father's book collection to the university as the Emil Fischer Library (73).

The sample collection served as a reference for ongoing research and, according to Hermann Fischer, "made possible numerous identifications of interesting compounds" (73). It was used by Melvin Calvin to identify substances in his work on the carbon pathway in photosynthesis (79). With Emil Fischer's convention for the stereochemistry of sugars, this was one of the primary sources of stereochemical reference information. Fischer's convention stood for 60 years before being shown to be correct in 1951 (80).

A set of 30 peptide samples from Fischer's collection was analyzed in 1951, 50 years or so after their preparation. Paper chromatography showed that only three of these contained small amounts of one of their constituent amino acids in addition to the peptide; the other 27 samples were uncontaminated (81). Hydrolysis and analysis of small samples of several of these peptides showed only the described components (81). This is a remarkable testament to the caliber of work done by Fischer and to the integrity of the collection.

After Hermann Fischer's unexpected death in 1960, the care of the Fischer compound collection was assumed by Clinton Ballou, who had joined Hermann Fischer's lab in 1950. Ballou worked on numerous metabolic intermediates, and become Professor of Biochemistry at Berkeley in 1955 (82). Ballou continued to receive requests for reference samples from the collection, which he would honor as appropriate (83).

The compound collection and the laboratory stool were finally repatriated in 1983 when they were donated to the Deutsches Museum in Munich after a correspondence between Berkeley's Horace Barker and Ernst Otto Fischer at the Technical University at Munich (78, 84). The A. W. von Hofmann/Emil Fischer laboratory stool resided in Hermann Fischer's office until his death (78), after which it was displayed prominently in the Barker Hall Library at UC Berkeley (83). After its repatriation to Germany it found its way into the laboratories of Ernst Winnacker, a former postdoc of Barker's, in the Institute of Biochemistry at the University of Munich (79).

Emil Fischer's accumulated documents—his correspondence, laboratory notebooks, and manuscripts—were donated in 1970 to UC Berkeley's Bancroft Library by Mrs. Hermann Fischer (3, 85). Emil and Hermann Fischer's books moved in 1983 to the Marian Koshland Bioscience and Natural Resources Library in the Valley Life Sciences Building on the Berkeley campus, where they reside as of this writing (86, 87).

The compound collection contains some 9000 samples in vials and stoppered test tubes. The samples are carefully hand-labeled and packed in cigar boxes (Figure 3); this method of storage greatly simplified the samples' safe transport through so many moves (78). Each box is labeled with the name of the co-worker who collaborated on the work (78). Hermann Otto Laurence Fischer describes in his memoir the unique indexing system

Figure 3. *A cigar box in Emil Fischer's compound collection with sealed test tubes containing compound samples prepared by Max Bergmann and Hans V. Neyman. Bergmann was a prominent member of the Fischer lab and did research on amino acids, sugars, and tannins; Neyman worked on furfural derivatives (3, 9). Photograph by Susanne Rehn-Taube. Copyright Deutsches Museum, Munich.*

used for his father's collection: one looks up the compound to retrieve in the Collected Works of Emil Fischer (Emil Fischer Gesammelte Werke) (19, 29, 46, 47, 72, 77, 88, 89), finds the co-worker who did research on the compound, and then locates the cigar box that is labeled with that co-worker's name to retrieve the sample (73). One thus finds samples pertaining to innovative research that provided a wide array of techniques in organic chemistry, elucidated the structures of important classes of chemicals, and laid the groundwork for modern biochemistry.

After an improbable journey that lasted more than a century, Emil Fischer's compound collection has returned to its homeland near the institution where Fischer began his career. Residing in the Deutsches Museum in Munich, the collection contains samples from Fischer's work on dyes, purines, carbohydrates, peptides and proteins, glycerides, glycosides, tannins, and barbiturates—work that shaped major areas of biological chemistry. It endures as a tangible reminder of Emil Fischer's enormous contributions to chemistry.

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