5 Preparing the Way to the Constitutional Structure of Bilirubin

By 1917, the great advances toward the structure of bilirubin of the preceding two decades had ground to a near halt as World War I exacted its toll and Oskar Piloty had died, leaving only William Küster and Hans Fischer as the major investigators. Küster continued research on bilirubin throughout the war years and until his death in 1929; between 1911 and 1920 seven of his 36 publications dealt with the pigment, while between 1921 and 1929 six of his 45 publications did. The work, while not insignificant, dealt mainly with the structure of Hämin (hemin) and improving the isolation and purification methods for bilirubin (387–391) that were subsequently adopted by Fischer. Yet, the structure of the latter pigment was apparently not far from his sight, and in the mid-1920s he had realized that his dipyrrylpyridylmethane structures ought to be abandoned in favor of structures more closely tied to his 1912 structure of hemin. While Küster pursued his apparent major interest in the chemistry of hemin through the 1920s, Fischer initiated a major synthesis effort toward its structure.

Hans Fischer, still early in his career and without a base for research after 1915, was seriously deterred from his scientific ambitions by the unhappy days of the World War I and its aftermath. His research suffered a hiatus after 1915 when World War I began to take its toll on university and medical school enrollments, and during his call to teach in Innsbruck and Vienna. Unlike Küster, Fischer was not able to resume research productively until after 1921, the year that he accepted a call to follow Heinrich Wieland as o. Professor of Chemistry at the TH-München. The research that recommenced left bilirubin on a “back burner,” however, while a major effort was marshaled toward the synthesis of hemin. Thus, among the 145 Fischer research papers published between 1921 and 1930, only eight concerned bilirubin directly, while the vast majority dealt with porphyrins. As Adolph Stern¹,

¹Adolph J.C. Stern was born on February 12, 1900 in Nuremberg and died on April 29, 1992 in New York. After completing studies at the Gymnasium in 1917 he served in Germany’s South Field Artillery in World War I until 1919. He enrolled in the TH-München to study chemistry and engineering to achieve the Diplom in 1923 and the Dr. ing. in 1925 in organic chemistry with Hans Fischer. After the habilitation he became a lecturer at the TH in 1933 and laboratory director. In 1935 he was promoted to a. o. Prof. and in 1940 published, as the only co-author with Hans
a Fischer student, noted in his Fischer lecture at a porphyrin conference in 1973 sponsored by the New York Academy of Sciences, the early 1920s was a period of intense activity, as Fischer brought his laboratory into being (392):

In 1921, Hans Fischer succeeded Heinrich Wieland and took over as head of the Organic-chemical Institute at the Technical University of Munich and immediately an extensive program concerning the systematic exploration of all aspects of the chemistry of pyrrole, bile pigments, porphyrins and related compounds was designed and undertaken. The chemistry of pyrrole, in spite of the large number of naturally occurring derivatives was, at this time, practically untouched. Fischer’s first major objective was to elucidate the structures of porphyrins with a view toward synthesizing hemin. In doing so, Fischer’s magnetic personality attracted and inspired a great number of graduate students who, from the very beginning of his work in Munich, were his devoted disciples and ready to do anything to cooperate in achieving Fischer’s goals. In a short time, the “Fischer School” was to become one of the most remarkable research groups in Germany and well known internationally. He trained numerous excellent chemists, many of whom became leaders in chemical industry and in academic careers at home and abroad. During the period 1921-1925, a very large number of new pyrrole derivatives were synthesized either by substitution methods or ring synthesis.

Even after 1930, when Fischer had won the Nobel Prize in Chemistry and had begun to solve the structure of bilirubin by total synthesis, he elected to pursue the structure of chlorophyll with greater dedication (392):

A decision had to be made about which direction to continue research – bilirubin or chlorophyll. After discussion with his coworkers, Fischer decided to go ahead vigorously to elucidate the structure of chlorophyll, but not forget the bilirubin problem.

From 1930 until his death in 1945, Fischer published another 275 or so papers, the majority aimed at the structure elucidation and total synthesis of chlorophyll, work that remained incomplete despite an enormous effort put forth during the disastrous era of National Socialism and destruction during World War II. Yet between 1930 and 1942, some 25 papers were directed successfully toward the structure elucidation and total synthesis of bilirubin, the latter a more difficult synthesis accomplishment than that of hemin and the second crowning scientific achievement of Fischer’s life.

In contrast to Küster, Fischer devoted an enormous amount of energy and every available resource to develop the fundamental organic chemistry of mono-, di-, and tetra-pyrroles during the 1920s. Although the first target was hemin, the synthesis expertise developed in that quest was to become the basis for the synthesis of bilirubin. What was the structure of hemin that Fischer set first in his synthesis sight?

Fischer, the second half of volume II (on chlorophyll) of Die Chemie des Pyrrols (4). In 1938, only days before the Anschluss, he fled the Third Reich for London and the U.S., where he worked first as a research associate at the Research Laboratory Children’s Fund in Detroit. In 1942, he joined Wagner College as Professor of Chemistry and served with great distinction in many capacities (chairman, 1950; dean, 1952; special assistant to the president) before becoming emeritus on September 1, 1970.