KEYNOTE LECTURE

# From Bio-organic Chemistry to Molecular and Synthetic Biology: Fulfilling Emil Fischer's Dream

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## Introduction

The following paper is intended to provide a broad context for many of the subsequent papers of the workshop. I will do this by reflecting on a century of development in one area of the discipline of chemistry, with a particular focus on what I am calling "Emil Fischer's dream." In 1915 Fischer envisioned a central aspect of the transformation of chemistry in the twentieth century, the development of an interdisciplinary approach to the chemistry of life that would not only result in greater insight into the nature of life, but ultimately allow human beings to change the nature of life itself.

A century later, I believe we can agree that Fischer's dream is being fulfilled, and as I will argue, the critical developments that have made this possible occurred precisely during the period of the workshop's primary focus, the 1920s-1960s. I will assess developments in this period, including the loss of German leadership to other nations and the increasingly significant role of Japanese chemists, within the broader context of the development of synthetic-chemical and biochemical technologies applied to the study of living nature during the 20$^{th}$ century as a whole. I would like to divide the era from 1915 to 2005 into three principal generations, the first of which was a generation of crisis bracketed by world wars. Key transitions to new generations occurred around 1945 at the end of the Second World War, and in the mid-1970s, with the advent of modern biotechnology and genetic engineering. It is surely not a coincidence that each of these transition periods was followed by a flood of crucial innovations in the chemistry of biology and natural products, as well as physical methods and instrumentation. Space will not permit more than some selected references to developments since the 1970s, including the most recent wave of innovation in the current generation beginning around 2005, which is characterized by the emergence of the new discipline of synthetic biology. I will conclude by mentioning some interesting developments related to this new discipline in our host institution, the Tokyo Institute of Technology.

## Emil Fischer's dream

Emil Fischer (1852-1919) was of course the second Nobel Prizewinner in Chemistry (1902), leading organic chemist of his day and a pioneer of the synthetic chemistry of natural products, director of the largest chemical institute in Germany, and by 1915 Vice President and most influential scientist in the leadership of the young Kaiser Wilhelm Society for the Advancement of the Sciences, today's Max Planck Society. The Society was creating a series of research institutes, with emphasis on the physical and biological borders of chemistry –

which reflected Fischer's own goals of promoting interdisciplinary collaboration outside the increasingly conservative German universities and academies.[1]

What was Fischer's dream? It was a vision he expressed both publicly and privately, especially in a lecture presented about one hundred years ago at the beginning of the second year of the Great War, which had devastated scientific life in Europe. Looking beyond the war and indeed beyond his own lifetime, he envisioned the fruits of collaboration between organic chemistry and biology in creating a discipline he called "synthetic-chemical biology."[2] What did Fischer envision by the phrase "synthetic-chemical biology"? Essentially it was the chemical understanding and control of living matter. Fischer's lecture and his other correspondence at the time effectively present a research program for the new discipline, which I would like to briefly summarize here.

- First: to understand the individual cell "not only as a machine that constructs and repairs itself, but also as a chemical laboratory of the most amazing kind," and its chemical interactions with other cells in an organism through the metabolic processes of life.[3]
- Second: to understand the origins, composition, function, and changes undergone by various chemical substances in these processes, in order to duplicate and where possible to improve upon the already highly efficient processes of intra-cellular synthesis.[4] Thus while a plant could produce carbohydrates from carbon dioxide in a matter of minutes and with almost 100% yield using the energy from sunlight, a chemist could only achieve "minute yields" by synthesizing those same carbohydrates in a chemical laboratory – which Fischer knew all too well, as his work in this field had led to his Nobel Prize.
- Third: to focus especially on the role of enzymes in achieving amazingly high yields in biosynthesis and fermentation processes, "with a view toward their artificial preparation or replacement."[5] In other words, synthetic enzymes and chemically modified microorganisms would be the key to controlled biosynthesis on an industrial scale of carbohydrates and proteins for food and other purposes, as well as products such as ammonia (by duplicating bacterial nitrogen fixation).[6]
- Finally: the total synthesis of the nucleic acids, and the introduction of artificial nucleic acids into cell nuclei, in order to "gain a radical chemical influence on the development of the organism" by altering "the chemical building material of the cell," so as "in a sense to trick (*betrügen*) it."[7] On the assumption that the mutations postulated by Hugo de Vries' theory of discontinuous evolution were related to

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1 Jeffrey Allan Johnson, *The Kaiser's Chemists: Science and Modernization in Imperial Germany*, Chapel Hill, N. C.: University of North Carolina Press, 1990, chs. 1-2; Robert E. Kohler, *From Medical Chemistry to Biochemistry: The Making of a Biomedical Discipline*, Cambridge, UK: Cambridge Univ. Press, 1982, ch. 1.

2 H. Emil Fischer, "Die Kaiser-Wilhelm-Institute und der Zusammenhang von organischer Chemie und Biologie" (presented 28 October 1915), in *Untersuchungen aus verschiedenen Gebieten*, ed. Max Bergmann, Berlin: Julius Springer, 1924, 797-809, on 808.

3 Fischer (note 2), 798.

4 Fischer (note 2), 799.

5 Fischer (note 2), 805-806.

6 Fischer (note 2), 804-805; for wartime efforts of the Germans along these lines cf. Robert Bud, "Molecular biology and the long-term history of biotechnology," in *Private Science: Biotechnology and the Rise of the Molecular Sciences*, ed. Arnold Thackray, Philadelphia: University of Pennsylvania Press, 1998, 3-19, on 7; Robert Bud, *The Uses of Life: A History of Biotechnology*. Cambridge, UK: Cambridge Univ. Press 1993, 45; Luitgard Marschall, *Im Schatten der chemischen Synthese: industrielle Biotechnologie in Deutschland (1900-1970)*, Frankfurt a.M.: Campus, 2000, 70-75.

7 Fischer (note 2), 808.

> chemical changes in the cell nucleus, Fischer intended to begin with experiments on "lower life forms," and he only half-jokingly called this "my lusting for creation."[8]

"And thus I see," he concluded, "half in a dream, the emergence of a synthetic-chemical biology that will transform the living world as fundamentally as chemistry, physics, and industry have done for so long with non-living nature."[9] Here then was Fischer's dream – to transform life itself, using chemical means to "trick" the cell into developing in an artificially-controlled way, or producing something other than it would "naturally" produce. It is a vision of a future whose realization we are currently witnessing, through what began as molecular biology and genetic engineering, but today encompasses much more diverse and precise methods in fields known as protein engineering, metabolic engineering, and synthetic biology. Note that none of these fields contains the word "chemical" in its name, yet I further submit that Fischer would have recognized them as the "synthetic-chemical biology" whose emergence he predicted in 1915.

In regard to this I would like to mention one other project Fischer had at that time: to synthesize a "giant" organic molecule and make it visible under an ultramicroscope (then the most powerful imaging device) by incorporating a "strongly fluorescent" compound. Fischer's target would have a molecular weight of 8,000.[10] That might hardly seem "giant" by today's standards, but it was twice the size of the largest "record molecule" he (let alone anyone else) had yet attained by total synthesis.[11] And that might have been enough to satisfy Fischer's doubts about the even larger molecular weights, up to 16,000 or more, that others had published for proteins. Sadly, his research was interrupted by the Great War that killed millions across Europe, including two of Fischer's three sons. Never in robust health, Fischer exhausted himself as a scientific and technical advisor in the service of his country's war effort. His death in 1919 left to future generations the dream of synthesizing giant fluorescent molecules, creating synthetic enzymes for artificial biosynthesis, and inducing mutations through artificial nucleic acids.

## Fulfilling Fischer's dream – or not: the work of later generations

### 1) The crisis generation, 1915-1945

The era of the first generation following Fischer's 1915 speech, the three decades until the end of the Second World War in 1945, can best be described as an era of crisis. A crisis is by definition a period of transition, but also a period of danger in which "normal" development becomes difficult if not impossible. This was certainly the case for Germany, but also even for countries like the United States, which was spared the worst impact of the world wars. The recognition gained by chemists as a result of the First World War, the "chemists' war," was at best a mixed blessing, because the association of chemistry with poison gas cast a stigma on the discipline, from which arguably its reputation has never fully recovered. In the 1920s the German economy itself never fully recovered from a hyperinflation followed by a

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8 Fischer to Adolf von Baeyer, 4 Aug. 1913, in Outgoing Letters, Box 4, Emil Fischer Papers, Bancroft Library, UC Berkeley, CA. As early as 1907 Fischer had, in a humorous speech to his students, envisioned a future chemist synthesizing artificial life, including a homunculus that could replace their professor. See "Festrede gesprochen bei dem Ausflug des chemischen Instituts ... am 20. Juli 1907," in Folder "Addresses 1906-1910," Carton 4, Emil Fischer Papers, cited in Joachim Schummer, *Das Gotteshandwerk: Die künstliche Herstellung vom Leben im Labor*, Berlin: Suhrkamp, 2011, 76, 219-220.

9 Fischer (note 2), 808; cf. Horst Remane, *Emil Fischer*, Leipzig: B. G. Teubner, 1984, 63; Ute Deichmann, "Crystals, Colloids, or Molecules: Early Controversies about the Origin of Life and Synthetic Life," *Perspectives in Biology and Medicine* **55/4** (2012): 521–42, on 531.

10 Fischer to Carl Duisberg, 27 June 1914, in Outgoing Letters, Box 4, Fischer Papers (note 8).

11 Kurt Hoesch, *Emil Fischer: sein Leben und sein Werk*, Berlin: Verlag Chemie, 1921, 475.

drastic stabilization of the currency in the aftermath of the First World War, which reinforced an attitude of austerity in the minds of German financial experts that has continued to the present day. The resulting limits on funding for science including chemistry became worse in the wake of the Great Depression beginning in 1929, and the renewed expansion of the discipline in the late 1930s came in the context of a National Socialist regime with a policy of rearmament and economic autarky. This ideological attitude also fostered an autarkic intellectual tendency among scholars and scientists, which seriously hampered the free exchange of ideas particularly with scholars of the "wrong" ethnicity, religion, or political outlook.[12] Similar tendencies occurred in other nations, including the Soviet Union and arguably also to some extent Japan during the wartime period 1937-1945. But the outcome was most detrimental to chemistry in Germany; as the discipline's ostensible world leaders, the Germans had the most to lose.

Consider the factors in this period that affected German chemists in Fischer's area, the structure and synthesis of biological molecules:

First, the problem of leadership: Fischer's death in 1919 robbed the University of Berlin and the Kaiser Wilhelm Society of his scientific leadership in the postwar crisis period. One possible successor, Richard Willstätter, was widely recognized as the leader of the next generation of German organic chemists. But Willstätter, who had left the Kaiser Wilhelm Society to succeed Adolf Baeyer in Munich in 1915, refused to come back to Berlin. The best-known of the Society's chemists, Willstätter's friend Fritz Haber, famous or infamous as the scientific leader of German chemical warfare, encountered highly influential opposition within the dye industry because he was a physical chemist and not deemed capable of contributing effectively to organic chemistry.[13] Little did his opponents realize that in the new era, organic and biological chemistry would increasingly depend upon physical methods and instruments, beginning with x-ray crystallography.

Willstätter in the early 1920s continued to be the most respected German organic chemist. But he developed a theory of enzymes as "small reactive molecules adsorbed on colloidal carriers" rather than proteins. Clearly uneasy with his results (which may have been due to impure samples), and at the same time depressed by the rising tide of anti-Semitism affecting his university (Munich was then the major center of Nazism), in 1924 he resigned his professorship with an open protest against his faculty's inability to ignore ethnic considerations in making appointments. He never again took a position or set foot in a laboratory (until late in 1938, when he realized that he would have to leave Munich to escape a concentration camp or worse, he remained in his home in the city and worked through an assistant, communicating by telephone).[14] By the late 1920s, however, the research of the American biochemists James B. Sumner at Cornell and John H. Northrop at the Rockefeller

[12] There is now a very large literature on the impact of National Socialism on German science. Some useful general historiographical considerations are in Margit Szöllösi-Janze, "National Socialism and the Sciences: Reflections, Conclusions and Historical Perspectives," in *Science in the Third Reich* ed. Margit Szöllösi-Janze, Oxford, UK: Berg, 2001, 1-35; for chemistry and biochemistry see the works of Ute Deichmann, esp. *Flüchten, Mitmachen, Vergessen: Chemiker und Biochemiker im Nationalsozialismus*. Weinheim: Wiley-VCH, 2001, and most recently Helmut Maier, *Chemiker im "Dritten Reich". Die Deutsche Chemische Gesellschaft und der Verein Deutscher Chemiker im NS-Herrschaftsapparat*, Weinheim: Wiley-VCH, 2015.

[13] Margit Szöllösi-Janze, *Fritz Haber 1868–1934: Eine Biographie*, Munich: C. H. Beck, 1998, 438-447.

[14] Richard Willstätter, *From my Life: The Memoirs of Richard Willstätter*, trans. Lilli Hornig from the 2d German ed. (Weinheim, 1958), New York: W. A. Benjamin, 1965, 360-367, 428-431; Freddy Litten, *Der Rücktritt Richard Willstätters 1924/25 und seine Hintergründe: ein Münchener Universitätsskandal?* München: Institut für Geschichte der Naturwissenschaften, 1999.

Institute demonstrated that enzymes were proteins.[15] This won them shares of the Nobel Prize in 1946, while undermining the authority both of Willstätter and, by extension, German structural biochemistry.

Fischer's closest associate in his final synthetic projects, Max Bergmann, had been unable to get a university position and in 1921 became director of the newly established Kaiser Wilhelm Institute for Leather Research in Dresden, where he investigated the chemistry of skin and continued the synthetic peptide and protein research begun in Berlin. This led to a major achievement in 1932 with the carbobenzoxy method developed by Bergmann and his associate Leonidas Zervas. This was the first effective means of synthesizing longer chains of peptides and integrating amino acids that were not susceptible to Fischer's earlier methods.[16] Bergmann also mentored a young American postdoc, Vincent du Vigneaud, who would later make a name for himself in protein synthesis.[17] But in 1933, the advent of the National Socialist regime forced Bergmann as a "non-Aryan" out of his position, so that he and Zervas (who was Greek) emigrated to the United States, where they continued their research in the Rockefeller Institute, enhancing its status as one of the major American biochemical research centers.

Second, funding limitations: As the postwar inflation had initially worsened in 1920, several institutions had been established to develop alternative sources of funding. Among these were the *Notgemeinschaft* (Emergency Association for German Science, later known as the *Deutsche Forschungsgemeinschaft* or German Research Foundation) co-founded by Fritz Haber with mainly federal government support, as well as the chemical industry's funding groups organized by Carl Duisberg of the Bayer Corporation. For the support of chemistry by the *Notgemeinschaft* in particular, an unexpected supplementary source came from Japan through the philanthropy of Hajime Hoshi, founder and president of the Hoshi Pharmaceutical Company (specializing in vaccines, alkaloids, and other natural products) and also founder of a pharmaceutical school that eventually became Hoshi University. Along with a larger endowment for German science in general, after meeting Haber in Berlin in the fall of 1922 Hoshi offered supplementary support for the physical sciences in 1922-25 in the amount of 2,000 yen or $1,000 per month, for which Haber organized the Japan Committee chaired by himself with Richard Willstätter as the vice chair, and several other top chemists and physicists along with government officials as members. This committee directed around a hundred grants to critical projects in a non-bureaucratic manner over two years, including Carl Neuberg's biochemical studies of sugar fermentation at the Kaiser Wilhelm Institute for Experimental Therapy.[18] Unfortunately the devastating Tokyo earthquake of Sept. 1, 1923, severely affected Hoshi's company and reduced his ability to extend his support, so that from 1924 the Japan Committee's more modest grants had to be matched by German government or industry funds. After 1925 the committee became inactive.

Haber and Willstätter sought to revive the Japan Committee in 1928, making an appeal to the German federal government by using a classic declinist argument: that German leadership in chemistry was threatened from abroad, particularly in the interdisciplinary fields on the borders with physics and biology. Funding was particularly vital in these fields, because on both sides of the discipline the growing significance of instrumentation and physical approaches – ultracentrifuges, x-ray apparatus, etc. – meant that cutting-edge research was increasingly expensive. By that time the declinist argument was becoming highly popular

[15] Joseph S. Fruton, *Proteins, Enzymes, Genes: The Interplay of Chemistry and Biology*, New Haven, Conn.: Yale University Press, 1999, 208.
[16] Fruton (note 15), 189.
[17] Deichmann (note 12), 258.
[18] Szöllösi-Janze (note 13), 363-364.

among German chemists, so that it was beginning to seem more than a rhetorical device. Despite promising beginnings before the war, and the establishment of some Kaiser Wilhelm Institutes related to biochemistry, the field was encountering institutional difficulties in the universities.[19] Even in the relatively prosperous years of the mid-1920s, academic institutes appeared to be underfunded, and the major German chemical associations had submitted memoranda to the government in the hopes of obtaining greater support. In regard to biochemistry, Haber and Willstätter asserted that Gemany had already lost its leadership to the "Anglo-Saxon lands," and that due to inadequate funds and a lack of qualified students, German laboratories saw themselves "mostly excluded from significant areas of biochemistry."[20]

Support for this view even came from abroad; in 1926 the British biochemist F. Gowland Hopkins had pointed out that "modern Germany provides but little institutional freedom" for biochemistry, warning that it would be "difficult to see how she can continue to lead along the path she has trod almost alone."[21] Haber and Willstätter therefore requested an additional 200,000 to 250,000 marks per year over the next five years to support strategic grants for physical and biochemistry. But such funds would not be forthcoming in the face of an imminent economic collapse that led to drastic austerity policies in Germany. By 1931 the new Kaiser Wilhelm Institute for Cell Physiology, under Emil Fischer's former associate Otto H. Warburg, had to receive its major support not from within Germany at all, but rather from the American Rockefeller Foundation.[22]

Impact of National Socialism: It is well-known that large numbers of Jewish or "non-Aryan" scientists (including both Willstätter and Haber as well as Bergmann) could no longer work in Germany after 1933. Chemistry and especially biochemistry were among the disciplines worst-hit by National Socialism, with more than one hundred dismissals, nearly one-quarter of those in academic positions in German institutions (or Austrian and Czech institutions in 1938).[23] One of the rare exceptions to this ban was Otto H. Warburg, who was allowed to continue to direct his Kaiser Wilhelm Institute and was able to keep up a high level of biochemical research (seeking a cure for cancer). But as Deichmann has shown, National Socialism tended to quash scientific debate and mute criticism of senior researchers, so that some of the leading "Aryan" researchers, including Emil Abderhalden and Adolf Butenandt (who avoided contact with Warburg), continued to advocate incorrect views with little opposition during this period. This further undermined the prestige and quality of biochemistry in Germany by 1945, with negative effects extending into the postwar era.[24]

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19 Kohler (note 1), ch. 1.

20 Fritz Haber and Richard Willstätter, "Denkschrift betreffend die Erneuerung des Japan-Ausschusses der Notgemeinschaft der Deutschen Wissenschaft," submitted to the President of the Notgemeinschaft, Friedrich Schmidt-Ott (signed Willstätter, Munich, Feb. 2, Haber, Berlin-Dahlem, Feb. 9, 1928). In: Geheimes Staatsarchiv Preußischer Kulturbesitz, Berlin-Dahlem, Rep 92 (Friedrich Schmidt-Ott), Nr. 43: 11-19, on 14.

21 Cited in Fruton (note 15), 57.

22 Fruton (note 15), 44. Cf. also Kristie Macrakis, *Surviving the Swastika: Scientific Research in Nazi Germany*, Oxford and New York: Oxford University Press, 1993, 63-64.

23 Deichmann (note 12), 106-107.

24 On Butenandt's uncritical support for the problematic and in part possibly fraudulent results of his friends Fritz Kögl and Emil Abderhalden in the field of cancer-related proteins and enzymes, see Ute Deichmann, "Proteinforschung an Kaiser-Wilhelm-Instituten 1930-1950 im internationalen Vergleich," *Ergebnisse: Vorabdrucke aus dem Forschungsprogramm "Geschichte der Kaiser-Wilhelm-Gesellschaft im Nationalsozialismus,"* 21 (Berlin: Max-Planck-Gesellschaft zur Förderung der Wissenschaften, 2004), 28-36; on Abderhalden see Ute Deichmann, "'I Detest his Way of Working'. Leonor Michaelis (1875-1949), Emil Abderhalden (1877-1950) and Jewish and non-Jewish Biochemists in Germany," in *Jews and Sciences in German Contexts: Case Studies from the 19th and 20th Centuries*, ed. Ulrich Charpa and Ute Deichmann, Tübingen: Mohr-Siebeck, 2007, 101-126.

The innovative role of x-ray crystallography, and its limits: It is of course true that a great deal of effort in German research centers during the 1920s went into the development of x-ray crystallography for structural analysis. This is a crucial innovation and one whose potential value for elucidating complex organic structures Emil Fischer was apparently unaware of in 1915. It is also remarkable that the first scientists to subject organic materials (natural fibers such as silk and wool) to x-ray crystallographic analysis, as early as 1913, were two young Japanese researchers at the University of Tokyo, the physics graduate students Shoji Nishikawa and S. Ono. The war prevented this from being followed up in Europe until the 1920s, though Nishikawa did influence American researchers during a visit to Cornell in 1916-19.[25]

X-ray crystallography showed that in the new generation, crucial advances would come not merely from the interaction of organic chemistry with biology (as Fischer had expected), but also and even more decisively from the collaboration of physical chemistry and physical instrumentation with biology. One can cite, for example, the work of the Kaiser Wilhelm Institute for Fibers Research in Berlin-Dahlem led by Rudolf Herzog, with several brilliant young scientists including Max Bergmann (before he moved to Dresden), Michael Polanyi, Hermann Mark and others.[26] It is worth noting that both Polanyi and Mark, as well as many of their young KWI colleagues, had come to Dahlem to escape from the chaos of the disintegrating Austro-Hungarian Empire and its successor states. In the revolutionary spirit of the immediate postwar era, these rebellious outsiders brought fresh ideas, creativity, and a willingness to defy established authorities, which led to dramatic improvements in the apparatus and methodologies, which were now being applied systematically to organic structures for the first time.[27] Organic chemists themselves, however, tended not to use this method, in part because it required sophisticated mathematical analysis; as one German physical chemist put it as late as 1938, "with a mixture of fear and repugnance, most chemists seek to avoid everything mathematical."[28]

But the main orientation of x-ray crystallography in the German and other European contexts at this time was related to the textile industry, especially cellulose fibers, and also inorganic crystals or metals rather than biologically significant molecules such as proteins or nucleic acids. The lack of attention to biologically active molecules applied not only to Hermann Staudinger and his macromolecular theory, whose origins have been well described by our colleague Yasu Furukawa, but also to Staudinger's main rivals after 1926, K. H. Meyer and Hermann Mark, whose theory of "polymers" (chiefly applying to cellulose, rubber and plastics) arose from collaborative research at the I.G. Farben works in Ludwigshafen (the once and future BASF corporation). During the 1920s, however, most organic chemists, even

[25] André Authier, *Early Days of X-ray Crystallography*, Oxford: Oxford Univ. Press, 2013, 136-137, 260. Note: this paper uses the Western style for Japanese names, with surnames following given names.

[26] Mary Jo Nye, *Michael Polanyi and His Generation: Origins of the Social Construction of Science*, Chicago: The University of Chicago Press, 2011; Jeremiah James et al., *One Hundred Years at the Intersection of Chemistry and Physics: the Fritz Haber Institute of the Max Planck Society, 1911-2011*, Berlin: De Gruyter, 2011; Ulrich Marsch, *Zwischen Wissenschaft und Wirtschaft: Industrieforschung in Deutschland und Grossbritannien 1880-1936*, Paderborn: Schöningh, 2000, 431-463 (for funding and organization of the fiber research institute).

[27] Michael Polanyi, "My Time with X-rays and Crystals," in Paul Peter Ewald, ed. *Fifty Years of X-ray Diffraction: Dedicated to the International Union of Crystallography on the Occasion of the Commemoration Meeting in Munich, July 1962*. Utrecht: Published for the International Union of Crystallography by A. Oosthoek's Uitgeversmij, 1962, 629-636 (http://www.iucr.org/publ/50yearsofxraydiffraction/full-text, accessed 2/24/2015).

[28] Cited in Jeffrey Allan Johnson, "The Case of the Missing German Quantum Chemists: On Molecular Models, Mobilization, and the Paradoxes of Modernizing Chemistry in Nazi Germany," *Historical Studies in the Natural Sciences*, **43/4** (2013): 391–452, on 440.

those dealing with organic products such as vitamins, continued to emphasize relatively small molecules; in Germany, many physical chemists such as Wolfgang Ostwald also advocated a colloidal aggregate theory.[29] Interestingly enough, it has been argued that the Staudinger vs. Meyer-Mark vs. colloidal aggregate controversies were largely irrelevant to protein chemists at the time, because most were already persuaded in effect that proteins were macromolecules, even before The Svedberg's ultracentrifuge provided more conclusive evidence against colloidal aggregates from 1926. The main issue was the details of protein structure.[30]

The structural question for proteins came to be a central focus of the work of the British physical scientist William T. Astbury, who from 1926 began to examine natural fibers including hair and wool. Like many of the Germans, he too benefited from a productive relationship with the local textile industry in Leeds. During this period, Leeds was a particularly fertile location for physical organic chemistry, as C. K. Ingold was also there (1924-30) before returning to University College London. Astbury's studies of natural fiber proteins in the 1930s, with a focus on keratin as a component of wool, led to proposals for two distinct structures, an α-form (coiled) and a β-form (stretched). These later inspired Linus Pauling and Robert Corey's protein structures after 1945. Nevertheless Astbury did not initially check his crystallography-based model against an organic-chemical, space-filling molecular model, so that in the late 1930s other scientists pointed out various weaknesses in the structural details of his model. Astbury was primarily a physicist and crystallographer, not an organic or biochemist, so that here again, despite his interest in the newly emerging interdisciplinary field of "molecular biology," his results were limited by a lack of full interdisciplinary collaboration. Similarly, with his pioneering examination of nucleic acids he did not seek to combine the crystallographic analysis with molecular model-building.[31]

**2) The Cold War generation, 1945-1975: unlocking the secrets of life**

The post-1945 generation began under the sign of global reconstruction following the most destructive war in history, but the process of postwar recovery was further complicated by the political division of the world with the advent of the Cold War between the contending superpowers, the USA and the Soviet Union. Historians are still investigating the details of how the aftermath of the Second World War may have affected the recovery of scientific activity, and of work in chemistry in particular, but it does appear that the victorious American and British scientific establishments emerged from the war with great prestige and public support. The opposite was true in Germany, not least because of the association of the chemical industry with National Socialist mass murder in Auschwitz. Along with other factors including the postwar division of the country and the removal of technical experts by both Soviets and Americans, as well as the reluctance of most interwar political emigrants to return to postwar Germany, this confirmed the loss of scientific leadership that the Germans had feared in the interwar era. Thus it was perhaps not coincidental that in the first postwar decade, the most significant developments in the chemistry of the proteins and nucleic acids occurred in the USA and Britain. In Japan, the situation was somewhat different. My impression is that in response to the American occupation and enforced demilitarization of the country, along with the war-related economic devastation and ensuing food shortages, the chemistry and industry of natural products appeared as a logical and desirable focus for many

[29] Authier (note 25), 261; Yasu Furukawa, *Inventing Polymer Science: Staudinger, Carothers, and the Emergence of Macromolecular Chemistry*, Philadelphia, Penn.: University of Pennsylvania Press, 1998; Claus Priesner, *H. Staudinger, H. Mark and K. H. Meyer: Thesen zur Größe und Struktur der Makromoleküle*, Weinheim: Verlag Chemie, 1980.

[30] Charles Tanford and Jacqueline Reynolds, *Nature's Robots: A History of Proteins*. Oxford: Oxford Univ. Press, 2001, 51-52, 59-60.

[31] Robert C. Olby, *The Path to the Double Helix*, Seattle: University of Washington Press, 1974, 63-70.

talented young Japanese scientists in the postwar era. Reviving and expanding trends already begun before the war, in the 1950s and 1960s a significant and productive academic-industrial symbiosis developed in pharmaceuticals and natural products such as vitamins, amino acids, and peptides. As I will mention later, and as some of the papers in our workshop discuss, the result would be a series of innovations by Japanese scientists, some of which would ultimately lead to Nobel Prizes and other awards.

First, however, let me discuss some of the best-known innovations by Anglo-American scientists in the post-1945 generation. Linus Pauling's alpha-helix model of protein structure is of course famous, and Mary Jo Nye's paper discusses Pauling's influence and his work leading up to this, so I need say little here.[32] I will point out that Pauling benefited from an interdisciplinary approach including the use of structural ideas derived from quantum theory and x-ray crystallography as well as physical model-building, in this case going far beyond the interwar protein scientists such as Astbury. One of the more advanced versions of the alpha-helix model employs space-filling molecular models of a type first developed in the 1930s by a German (and National Socialist) physicist, H. A. Stuart, who had apparently in part been inspired by Pauling's earlier work employing quantum ideas to elucidate molecular structures. But the use of the models by German organic chemists was quite limited.[33]

Given a new model of protein structure, an organic chemist would want to confirm it by synthesis. A crucial breakthrough came in 1953, which everyone knows was the year of the double-helix model of DNA. Only specialists are aware of the total synthesis of oxytocin by Vincent du Vigneaud, which was nevertheless so significant that he became the sole winner of the Chemistry Nobel Prize in near record time – only two years later – in 1955. What was the significance of this achievement? It was the first synthesis of a polypeptide hormone, following the Bergmann-Zervas carbobenzoxy process developed a generation earlier. But although that process was effective and came "universally" into use among peptide chemists after this success, it was also "difficult and time consuming," which inspired young chemists to develop newer, faster and more productive methods of peptide and protein synthesis.[34] Here I will mention two of these new methods.

In 1959 Robert Bruce Merrifield at the Rockefeller Institute had the idea for one of these new methods, the "solid phase peptide synthesis." This he described in a sole-authored paper in the *Journal of the American Chemical Society* in 1963, which became one of the most often cited in the journal's history.[35] He and a colleague went on to effect the first synthesis of the enzyme Ribonuclease A in 1969. Ultimately Merrifield's new, highly influential method brought him the honor of a sole Nobel Prize in Chemistry in 1984. A crucial feature of Merrifield's process was that, as he put it in his Nobel Lecture, it could be "mechanized and automated," a goal he had already announced in his 1963 paper. Thus for the first time, it would be possible to commercially mass-produce peptides using various types of machines,

[32] Mary Jo Nye, "A Career at the Center: Linus Pauling and the Transformation of Chemical Science in the Twentieth Century," in the present volume.

[33] Johnson (note 28), 401-412; H.-J. Schneider (personal communication by courtesy of Stephen J. Weininger), 2015.

[34] Robert Bruce Merrifield, "Solid Phase Synthesis" (Nobel lecture, 8 December 1984), in: *Chemistry, 1981-1990*, ed. Tore Frängsmyr and B. G. Malmström (Singapore: World Scientific, 1992); series: Nobel Lectures, Including Presentation Speeches and Laureates' Biographies, 149-174, on 149.

[35] R. B. Merrifield, "Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide," *Journal of the American Chemical Society* **85** (1963): 2149–2154.

developed in several different countries.[36] This foreshadowed many later devices used in genetic engineering and modern biotechnology.

During the same period in Japan, the biochemist Shumpei Sakakibara was just beginning his research career at Osaka University in the early 1950s. His first project was to attempt to replicate du Vigneaud's 1953 synthesis. Although he was only partially successful, it was a starting point for his further research leading to the development of a methodology for the solution synthesis of proteins, which may be considered an alternative to the Merrifield solid-phase process.[37] As is well-known to Japanese historians of chemistry, Sakakibara became head of the Peptide Center of the Osaka Institute for Protein Research, which had been founded in 1959 under the later president of Osaka University, Shiro Akabori. The Peptide Center synthesized a long series of biologically active peptides, the first to be produced in Japan and an important stimulus to the expansion of Japanese peptide and protein research. Ultimately Sakakibara became head of the Protein Research Foundation (PRF), which took over responsibility for peptide production from the Osaka Institute when the demand became too great.[38] The PRF came to be supported by a dozen or so of the leading Japanese chemical, pharmaceutical, and natural-products firms, some of which date to the era before the First World War. Hence it may be considered an exemplary model of a successful academic-industrial symbiosis in the Japanese context.[39] As a student of the original German version of this symbiosis established in the dye industry during the late nineteenth century, I suspect that a comparative study of the German and Japanese cases would be of great interest.

Returning to the Anglo-American context of biological chemistry in the postwar era, I note that the history of the double helix model of 1953 is so well-known that a brief mention will suffice here. As with Pauling's alpha helix, the model produced by James D. Watson and Francis Crick is a product of modern structural organic chemistry, and it exemplifies the interdisciplinary nature of the new "molecular biology." It was, of course, based on the work of a physical chemist and x-ray crystallographer, Rosalind Franklin, who produced the famous image of the B-form of DNA from which the biologist Watson and the physicist Crick deduced (without acknowledgment) much of the details of the structure, with the help of advanced mathematics in the form of Fourier analysis. Moreover, the organic chemist Jerry Donohue provided crucial assistance to them in working out the structural details of the base-pairings, the idea for which derived from the work of the biochemist Erwin Chargaff.[40]

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[36] Merrifield (note 34), 156; Merrifield (note 34), 2149; cf. Robert Bruce Merrifield, *Life during a Golden Age of Peptide Chemistry: The Concept and Development of Solid-Phase Peptide Synthesis.* Washington, DC: American Chemical Society, 1993.

[37] Shumpei Sakakibara, "Fifty years of my Protein Synthesis," in *Frontiers of Peptide Science*: *Proceedings of the Fifteenth American Peptide Symposium June 14–19, 1997, Nashville, Tennessee, U.S.A.*, ed. James P. Tam and Pravin T. P. Kaumaya, Dordrecht, NL: Kluwer, 1999, 1-10, on 1-2.

[38] Terutoshi Kimura, "Message from Chairman of the Board" (Protein Research Foundation: https://www.prf.or.jp/aisatsu-e.html, accessed 2/18/2015; Fruton (note 15), 78.

[39] Firms listed with links to their websites and corporate histories at: https://www.prf.or.jp/sanjo-e.html, accessed 2/18/2015.

[40] For this well-known but controversial episode of modern science, see various accounts including Fruton (note 15), 392-454; Horace Freeland Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology*, New York: Simon and Schuster, 1979; Erwin Chargaff, *Heraclitean Fire: Sketches from a Life Before Nature*, New York: Rockefeller University Press, 1978; Olby (note 31); James D. Watson, *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*, ed. Gunther S. Stent, New York: Norton, 1980 (Norton Critical Edition of *The Double Helix*, orig. publ. New York: Atheneum, 1968); Brenda Maddox, *Rosalind Franklin: The Dark Lady of DNA*, New York: HarperCollins, 2002; Maurice Wilkins, *The Third Man of the Double Helix: Memoirs of a Life in Science*, Oxford, UK: Oxford University Press, 2003.

While Watson and Crick's double helix continues to be celebrated in the popular press, I would prefer to emphasize a far less popularly known pioneering achievement in DNA chemistry, yet one that stands more directly in Emil Fischer's tradition. This was the Nobel Prize-winning work of the American biochemist Arthur Kornberg (1918-2007) who, beginning in 1955, isolated the first DNA polymerase enzyme, the enzyme that played a central role in the actual construction of DNA. With it he could test the Watson-Crick model of the double helix. This required a difficult process of purification of the enzyme, without which the DNA it produced would have serious defects and remain inert.[41] In 1967 Kornberg finally achieved Fischer's elusive goal of synthesizing biologically active DNA from its components, by using the polymerase to build a single strand of Phi X 174 viral DNA. He thereby became the subject of global headlines about "life created in the test tube." Although Kornberg noted that producing a strand of viral DNA was hardly the same as creating an artificial organism, nevertheless he later recalled that he felt like an observer of the first nuclear detonation in 1945; both were equally revolutionary events.[42] He had demonstrated the biological activity of the synthetic DNA by infecting the E. coli bacterium, which was already well on its way to becoming a favored vehicle for genetic experimentation. Kornberg's thinking and language, as cited in 1969, was remarkably similar to Fischer's, a half-century earlier, when he had spoken about using artificial nucleic acid to "trick" an organism: "If we know how to use this enzyme [polymerase] to copy this particular virus then we can copy other viruses, and . . . we can modify their structure by putting in alternative or *fraudulent* building blocks to create new forms of the virus. We can then use the synthetic virus to infect cells and produce altered responses. . . . We can look forward to the correction of genetic defects." In other words, Kornberg was looking toward gene therapy with the help of what was now being called "genetic engineering," which would spark a biotech boom in the next generation.[43]

**3) The millennial generation, 1975-2005: from molecular biology to synthetic biology**

Space does not permit a full discussion of the emergence of genetic engineering, protein engineering, and metabolic engineering as exemplars of the new academic-industrial symbiosis in the post-1970s generation, but I would like to mention research on Green Fluorescent Protein (GFP) and its analogues. Osamu Shimomura's work on GFP is discussed in this workshop by my esteemed colleague Masanori Kaji.[44] Shimomura was of course honored by the 2008 Nobel Prize in Chemistry, along with two younger Americans, Martin Chalfie and Roger Tsien. These three men represent the transition from the post-1945 to the post-1970s generation. Chalfie and Tsien in particular reflect how scientific work on the chemistry of life became both far more collective and far more interdisciplinary than in the pre-1970s generations.[45] Their work on fluorescent proteins made these into ubiquitous and variegated tools of synthetic biology. Like the 19th century "rainbow makers" of the synthetic dye industry who produced thousands of artificial colors, today's rainbow makers, epitomized by Tsien and his colleagues, have created a "fluorescent protein paintbox."[46] And recalling

41 Arthur Kornberg, "The Biologic Synthesis of Deoxyribonucleic Acid" (Nobel Lecture, December 11, 1959), in: Nobel Foundation (Stockholm), *Nobel Lectures, Physiology or Medicine 1942-1962*, Elsevier Publishing Company, Amsterdam, 1964, 665-680, on 670.

42 Arthur Kornberg, "Never a Dull Enzyme," *Annual Reviews of Biochemistry* **58** (1989):1-31, on 14.

43 Cited in Fred Warshofsky, *The Control of Life*, New York: Viking Press, 1969 (Series: The 21st Century), 35-36 (emphasis added).

44 Masanori Kaji, "The Transformation of Organic Chemistry in Japan," in the present volume.

45 Roger Y. Tsien, "Constructing and Exploiting the Fluorescent Protein Paintbox" (Nobel lecture December 8, 2008), in: *Les Prix Nobel. The Nobel Prizes 2008*, ed. Karl Grandin, Stockholm: Nobel Foundation, 2009, 186-214.

46 Tsien (note 45), Fig. 12; cf. Anthony S. Travis, *The Rainbow Makers: The Origins of the Synthetic Dyestuffs Industry in Western Europe*. Bethlehem: Lehigh University Press, 1993.

Emil Fischer's effort to create a visible fluorescent molecule by total synthesis, it is worth noting that in 1998 Shumpei Sakakibara and his team, using a version of the solution-synthesis technique they had first described in 1981, reported the total chemical synthesis of the precursor molecule of natural green fluorescent protein and its conversion to GFP.[47]

**4) The contemporary generation: fulfilling Fischer's dream?**

I would like to conclude by briefly touching on the new generation that has begun to emerge in the 21st century, particularly in regard to the still forming and developing interdisciplinary discipline known as "synthetic biology."[48] The practitioners in this discipline whom I have recently interviewed look forward to the engineering of living systems in a systematic way, going well beyond the older "genetic engineering," which from their perspective is not "engineering" at all because it cannot mas-produce in a standard way with predictable results. Going even beyond Fischer's dream of a "synthetic-chemical biology," today's practitioners come from an amazing range of professional and disciplinary backgrounds including electrical engineering and artificial intelligence, each with a somewhat different goal or even definition of the discipline. Part of it clearly fulfills Fischer's dream: the total synthesis of artificial chromosomes, a difficult project but with a few promising recent achievements such as the creation of "synIII," an artificial but functional yeast chromosome.[49] Yet at the opposite end of the spectrum is a project promoted by some of its advocates such as Drew Endy and Tom Knight, which has captured the attention of young people on a global scale through the International Genetically Engineered Machine (iGEM) competition. In this, teams of undergraduates are given so-called "BioBricks" – a "set of standard and reliable engineering mechanisms" for use in the "assembly of genetic components into larger systems" – to carry out synthetic biology projects.[50]

But I hardly need to describe this here, because Tokyo Tech has been one of the most successful institutions in the iGEM competition in recent years. Its Information Processing team can boast of winning the world iGEM competition in its division for the past three years in a row, a feat equaled by no other university in the world.[51] I am pleased to have had the opportunity while at the Tokyo Institute of Technology to speak with some of those involved in this work, which strikes me as something which the German chemists of the nineteenth century would have applauded: for had not the great Justus Liebig demonstrated that the best way to learn chemistry and to promote chemical creativity was through doing chemistry in a laboratory? So I salute my colleagues of Tokyo Tech, and its bright, hardworking, and ingenious students. Perhaps one among them will be a Nobel Prizewinner in future years, and

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47 Yuji Nishiuchi et al., "Chemical Synthesis of the Precursor Molecule of the *Aequorea* Green Fluorescent Protein, Subsequent Folding, and Development of Fluorescence," *Proceedings of the National Academy of Sciences of the United States of America* **95.23** (1998): 13549–13554; T. Kimura et al., "Strategy for the Synthesis of Large Peptides: An Application to the Total Synthesis of Human Parathyroid Hormone [hPTH(1–84)]," *Biopolymers* **20** (1981): 1823-1832; Shimpei Sakakibara, "Chemical Synthesis of Proteins in Solution," *Biopolymers* **51/4** (1999): 279–296.

48 Luis Campos, "Outsiders and In-Laws: Drew Endy and the Case of Synthetic Biology," in *Outsider Scientists: Routes to Innovation in Biology*, ed. Oren Harman and Michael Dietrich, Chicago: University of Chicago Press, 2013, 331-348.

49 Narayana Annaluru et al. (80 co-authors), "Total Synthesis of a Functional Designer Eukaryotic Chromosome," *Science* **344/6179** (4 April 2014): 55-58.

50 Luis Campos, "The Biobrick™ Road," *Biosocieties* **7.2** (June 2012): 115-139; quotation from Tom Knight, *Idempotent Vector Design for Standard Assembly of Biobricks*, Cambridge, Mass.: MIT Artificial Intelligence Lab / Synthetic Biology Working Group, 2003, 2 (http://hdl.handle.net/1721.1/21168, accessed 2/20/2015).

51 Tokyo Institute of Technology, "Tokyo Tech Students Win at iGEM Three Years in a Row," *Tokyo Tech News* (January 21, 2015) (http://www.titech.ac.jp/english/news/2015/029586.html, accessed 2/18/2015).

for this reason they deserve to be placed in the company of Emil Fischer, Linus Pauling, and Osamu Shimomura.

## Postscript

While the preceding paper has generally taken a positive perspective on the work on chemists, biochemists, and synthetic biologists since Emil Fischer, it should not be forgotten that Fischer's idea of gaining "a radical chemical influence on the development of the organism"[52] may raise fundamental problems for many observers, including scientists, when the organism in question is human. A recent publication by Chinese scientists has indeed presented serious ethical and practical questions about the appropriateness of seeking, for the first time in world history, to "edit" the human genome at the zygote stage during the process of in vitro fertilization, using currently available techniques. The goal was to produce permanent modifications to a single gene (with no unintended changes to others), which would also be capable of being transmitted to descendants. Unfortunately, as the Chinese acknowledged, the experiments were essentially failures and produced numerous unintended, damaging modifications of the genomes of the 85 embryos used (which would not have been viable in any case).[53] One of the authors claimed that both *Nature* and *Science* refused to publish their paper; if so, it would not be surprising, as both journals have publicly warned against this type of human experimentation.[54] It is also not surprising that online comments on news reports of these experiments used phrases like "mad scientists, "Frankenstein," and "Brave New World," using these iconic cultural images to express a deep distrust of human genetic experimentation.[55] To these commenters, perhaps Emil Fischer's dream would seem more a nightmare. Hence the larger project, of which my present paper is a part, will discuss not only the scientific and technical developments, but also explore the fundamental cultural issues raised by the emergence of technologies of artificial life.

**Acknowledgments**: part of the research for this paper was completed with support from a Haas Fellowship at the Chemical Heritage Foundation (CHF), Sept. 2014; my thanks to the fine staff of that institution for their support of my research. I also presented an early version of this paper as a Brown Bag Lecture to CHF on Sept. 30, 2014; my thanks to the participants in that colloquium, along with special thanks to the participants in the Tokyo Workshop in which I presented this paper, for many helpful comments and suggestions.

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52 Fischer (note 2), 808 (cited above, note 7).

53 Puping Liang et al., "CRISPR/Cas9-mediated Gene Editing in Human Tripronuclear Zygotes" *Protein & Cell* (18 April 2015), DOI 10.1007/s13238-015-0153-5 (open access; accessed 4/30/2015), print publ. **6/5** (May 2015): 363-372.

54 David Cyranoski and Sara Reardon, "Chinese Scientists Genetically Modify Human Embryos," *Nature / News* (22 April 2015) (http://www.nature.com/news/chinese-scientists-genetically-modify-human-embryos-1.17378#/b1 (accessed 4/30/2015)).

55 Examples: comments by "Bandylion," "KB," W. Wolfe, and William LeGro on the article of Gina Kolata, "Chinese Scientists Edit Genes of Human Embryos, Raising Concerns," *New York Times* (23 April 2015) (http://www.nytimes.com/2015/04/24/health/chinese-scientists-edit-genes-of-human-embryos-raising-concerns.html?_r=0, accessed 4/24/2015); comment by Dr. Upinder Fotadar on the Cyranoski & Reardon article (note 53).