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Jim's View: What makes transformative basic science possible?

In the previous essay in this series, I chronicled the extraordinary impact that the basic medical sciences have had on the human condition over the past century. This essay attempts to identify the key ingredients that enabled scientists to produce such transformative outcomes, focusing on the decades of fundamental research into cholesterol that yielded the statin drugs to control high blood cholesterol, and thus the risk of atherosclerosis. The third and final essay in this series will appraise the prospects and challenges for sustaining such productive basic sciences in current societal environments.

The cholesterol story teaches us the importance of a long-term and deeply embedded scientific culture. The story of how this happened (Fig. 1) was a triumph of the basic biochemistry and cell biology and illustrates much about the pre-conditions for success of our enterprise.

The first statin drug was approved in 1987, and like all statins it targets a rate-controlling enzyme in cholesterol biosynthesis, HMG-CoA reductase. The prototype of this drug was a natural product isolated from a screen of fungal extracts by Akira Endo in the 1970s. The rationale that a selective inhibitor of this enzyme could control the level of LDL cholesterol in the blood came from Michael Brown and Joseph Goldstein's contemporaneous discovery of the body's mechanisms to control cholesterol homeostasis via the LDL receptor, and in particular that when statins lower reductase activity and cholesterol production wanes, cells place additional LDL receptors on their surfaces.

Statins thus harness a normal mechanism by which cells drain cholesterol from the blood, yet ensure a steady supply of the molecule internally for vital activities. Their discovery that mutated LDL receptors underlie a rare genetic disorder in which LDL is elevated and atherosclerosis develops aggressively, even in childhood, provided a vital causal link to underscore years of epidemiological correlations that elevated LDL cholesterol may promote atherosclerosis in the general population.

Brown and Goldstein are physician-scientists who insightfully used a clinical genetic starting point to develop the underlying basic science. Their ability to navigate through what was at the time a fog of cell biology and physiology stemmed from the detailed knowledge of the biosynthetic pathway of cholesterol, mainly pieced together by Konrad Bloch and Fyodor Lynen in the 1950s, including the discovery of what emerged as the successful target, HMG-CoA reductase by Lynen.

Bloch, a war émigré, was trained in Germany and Switzerland as a chemist. He was motivated by the daunting complexity of cholesterol, a large hydrophobic molecule with many asymmetric stereo-centers. How could such a remarkable backbone be constructed from simple, symmetric two carbon units? He was not motivated by the (unknowable at the time) translational potential of the project.

Arriving in the US in 1936, Bloch completed his PhD degree at Columbia, then began postdoctoral research with Rudolph Schoenheimer (another German émigré at Columbia), who had just discovered how selective isotope labelling (then with deuterium) could be used to trace biosynthetic pathways. Utilizing this and later radio-isotope labelling methods ultimately enabled Bloch to discover the biosynthetic pathway and the enzymes responsible.

Bloch and Lynen could not have succeeded without two key insights that made the problem tractable. The first was the fundamental discovery of the mechanism of activation of carbon scaffolds for biosynthesis using Coenzyme A, made by Lynen and Fritz Lipmann (yet another German émigré to the US). The second insight was the common origin of the entire carbon backbone of cholesterol (and indeed the carbon skeletons of all steroids and even plant terpenes) from the same five carbon units (isoprene) found in rubber, greatly simplifying the scope of the problem.

The latter insight actually came much earlier from natural product structural chemistry in the 1920s and early 1930s, most especially from Butenandt and Ruzicka, in Germany and Switzerland respectively, and the related discovery of the sex hormones. They, in turn, depended on prior knowledge of the overall chemical structure of cholesterol and the related bile acids, thanks to the earlier research of Wieland and Windaus, both in Germany.

This summary focuses on just the highlights of a web of interconnected basic research spanning much of the 20th century that resulted in one of the most profound advances in public health in human history. The course of this research was largely unpredictable. It was a long-term process enabled by a broad and deep understanding of the underlying basic life science. Success depended vitally on meaningful and stable government support for investigator-initiated science, especially in Germanic Europe in the first half of the 20th century and then in the USA in the second half of the century. This historic transition began when the then world-renowned culture of German biochemistry was literally transplanted to America in the 1930s, and accelerated when the NIH began to offer meaningful extramural research grants in the 1950s.

Importantly, this success story relied on a deep multi-generational culture of masters and apprentices. For example, Lynen trained with Heinrich Wieland. As he wrote in his Nobel lecture (1964) “my subsequent concern with the problem of the acetic acid metabolism arose from my studies in Heinrich Wieland’s laboratory (1)”. Bloch also studied first with Wieland in Munich, then, as mentioned, with Schoenheimer in the USA. Schoenheimer himself was educated in Berlin (in Medicine and Chemistry) before emigrating in 1933 to New York where he worked with Harold Urey, who earlier had discovered deuterium.

Such un-programmable juxtapositions enabled Schoenheimer to link deuterium isotope labeling to metabolism, and later led Bloch to utilize this technique to dissect cholesterol biosynthesis. In fact, this lineage extends back to at least the German dye chemists in the late 1800s, as elegantly summarized by Hans Krebs (2) and continues to the present (including myself).

References

1. Feodor Lynen – Nobel Lecture. NobelPrize.org. Nobel Media AB 2019. Tue. 7 May 2019. <https://www.nobelprize.org/prizes/medicine/1964/lynen/lecture/>

2. Krebs, H. Nature 215:1441-1445 (1967)