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Heterotrophic CO_2-Fixation, Mentors, and Students: The Wood-Werkman ReactionS

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> Sir Gawain asked, "Sir, do you know the forest? What adventures may be we hope to find?"
>
> "I do not know it," said Marhalt. "If I did, it would not be adventure. But knights who have passed by have told me that it shelters wonders."[1]

Introduction

In *Science as a Process,* David Hull asserts that "science is a selection process."[2] What he intends by this statement is that scientific knowledge is accepted through a process that is only partially driven empirically. Of course, for ultimate acceptance, any scientific proposal must provide a means to test its assertions about the empirical world and must generate clear evidence that it accurately describes that world. While science shares many attributes with other human intellectual activities, nevertheless, as Hull states, "in no other area of human endeavor is the notion of 'evidence' so clear and direct" as in science.[3] Despite the importance of testable evidence, Hull contends that conceptual validation requires temporal and social aspects in the practice of science that go beyond obligatory empirical testing: "In the ongoing process of science, the inherent worth of ideas is far from irrelevant; but it is also far from sufficient, . . . being 'right' is not enough. Scientists must convince their fellow scientists as well."[4] Thus, Hull portrays science as a process of

[1] J. Steinbeck, *The Acts of King Arthur and His Noble Knights,* ed. C. Horton (New York: Noonday Press, 1993), p. 136.
[2] D. L. Hull, *Science as a Process* (Chicago: University of Chicago Press, 1988), p. 18.
[3] Ibid., p. 27.
[4] Ibid., p. 114.

the human intellect that in some respects resembles the biological process of natural selection.

While Hull is not alone in this claim, another important feature of his picture of science is its communal nature. The structure of science is such that individual scientists must continuously use the work of others. *Success* in science accrues to those individuals who are best at (a) evaluating and using relevant ideas of other scientists, and (b) having other scientists use their own ideas. Philip Kitcher stated: "Science is not done by logically omniscient lone knowers but by biological systems with certain kinds of capacities and limitations."[5] For Hull, a major manifestation of science's communal nature is the manner in which scientists collaborate with each other on problems of common interest. Jane Maienschein has observed that scientists collaborate for three broad reasons: to obtain assistance in order to work more efficiently; to gain credibility associated with the collaborator's credentials or prestige; and/or to create research communities that may be more able to attract resources than any of the individuals working in isolation.[6] She further notes that an important aspect of scientific collaboration is that between professor and student.[7] This particular form of mentoring collaboration is perhaps most crucial for the overall nature of science because it is the "training ground" for future scientists.

Most research scientists develop their *style of practice* during this apprenticeship, or mentoring, process. Junior scientists, usually trained in the fundamentals or basic factual information of the discipline, work under the supervision of a senior scientist on a research investigation, generally of common interest. The process serves two purposes: to teach research skills, and to socialize students to the "practice of science" by introducing them to the professional mores and social values of science. The relationship is, or at least ought to be, symbiotic: *students* simultaneously learn fundamental research methods, hone basic research skills, and develop "social skills" appropriate to the discipline; *mentors* benefit from the process by having a readily available supply of laboratory workers who are bright, energetic, generally younger, and (perhaps most important for many researchers) inexpensive. Students learn the "practice of science" in the mentoring process; however, mentors' careers often derive great benefit from their students' labors. An energetic and highly productive student can significantly affect a mentor's career. Furthermore, some mentors derive great personal satisfaction from working closely

[5] P. Kitcher, *The advancement of Science: Science without Legend, Objectivity without Illusions* (New York: Oxford University Press, 1993), p. 59.

[6] J. Maienschein, "Why Collaborate?" *J. Hist. Biol., 26* (1993), 167.

[7] I intend the notion "student" here in its most generic sense to include undergraduate research assistants, graduate students, and postdoctoral associates.

with their research associates. For Arthur Kornberg, for instance, "The most rewarding teaching . . . has been in the intimate daily contact with graduate and postdoctoral students."[8]

Like all human interactions, the mentoring styles – "the distinctive modes of thought and action" – of individuals vary greatly and are highly idiosyncratic.[9] Styles vary from a militaristic, dictatorial regulation, in which mentors control virtually every action of their associates, to liberal, free, and open interactions, in which mentors and associates operate on a more equal basis. For example, the American chemist Henry Gilman "expected total dedication: students were required to be in the laboratory working every day, including Sundays, late into the night."[10] Hans Krebs has observed that while Otto Warburg's laboratory rule was both fierce and autocratic, it was also benevolent in that Warburg never exploited his associates. Krebs further commented that "democratic rule may at best make full use of the pooled resources but at worst it may create a situation where ignorance and obstruction prevails over competence and efficiency."[11] Balance between the polarity of research leadership, as Joseph Fruton has noted, often is contingent not only on a mentor's personal and scientific abilities but also on external social factors such as the "social relevance" of a particular discipline, as well as broad "general social influences in different nations or institutions."[12]

The Wood-Werkman ReactionS

The term "ReactionS" in my title refers to (1) the professional interaction between Professor Chester Hamlin Werkman and his student (and later post-doctoral associate) Harland Goff Wood; and (2) the biochemical process of heterotrophic CO_2-fixation, which they discovered. In this essay, I have two primary objectives. First, I want to illustrate how a mentor-student interaction can be an evolutionary force to potentially shape a new scientific concept. Second, in showing the evolution of this new scientific concept, I want to describe one way a mentor-student collaboration can develop, as an example of ways that scientists interact with each other. My discussion here is

[8] A. Kornberg, *For the Love of Enzymes: The Odyssey of a Biochemist* (Cambridge, Mass.: Harvard University Press, 1989), p. 301.

[9] J. S. Fruton, *Contrasts in Scientific Style* (Philadelphia: American Philosophical Society, 1990), p. 2.

[10] C. Eaborn, "Henry Gilman," *Biograph. Mem. F.R.S., 36* (1990), 155.

[11] H. A. Krebs and F. A. Lipmann, "Dahlem in the Late Nineteen Twenties," in *Lipmann Symposium: Energy, Regulation and Biosynthesis in Molecular Biology*, ed. D. Richter (Berlin: Walter de Gruyter, 1974), p. 11.

[12] Fruton, *Scientific Style* (above, n. 9), p. 2.

specifically influenced by Hull's view of science described above. In that perspective, social pressures play a selective role in the acceptance or rejection of a scientific theory.[13] The collaboration between student and mentor is a powerful social relationship and potentially can foster or impede general acceptance of new scientific concepts. Thus, the relationship between student and mentor can be one of the initial selective pressures on a novel scientific concept.

Origin of the Wood-Werkman Reaction

The Protagonists: C. H. Werkman and H. G. Wood

Chester Werkman was born on June 17, 1893, in Fort Wayne, Indiana. He obtained a B.S. in chemistry at Purdue in 1919, and then worked in various chemical jobs for a few years before returning to graduate school at Iowa State and completing a Ph.D. in bacteriology (with R. E. Buchanan) in 1923. After a brief faculty appointment in Massachusetts, he returned to Iowa State as a faculty member in 1925 and remained there until his death in 1962. At Iowa State his research work was primarily focused on the chemical activities of bacteria. According to his biographer, R. W. Brown, "Werkman viewed bacteria . . . as the least complicated models for the study of the basic chemical transformations involved in living processes."[14] While this statement is accurate for Werkman's later career, his early research involved developing methods of organic chemical analysis or very traditional bacterial systematics. During the early 1930s, however, his interest in microbial metabolism began to flourish and reflected the influence of the Delft microbiologist A. J. Kluyver, who was a "Visiting Professor of Bacteriology and Chemistry" at Iowa State during part of 1932.[15] During the spring and summer terms Kluyver delivered an extensive series of lectures on the "physiology and biochemistry of bacteria," and his notes reflect his evolving vision that all living organisms are unified by common biochemical mechanisms and metabolic processes.[16] This was a biological perspective that guided the rest of Werkman's career, as well as the careers of his students.

[13] The notion of "social pressures" can have two meanings for science: there are pressures that arise from the peculiar context, practice, and structure of science itself; and there are also broader pressures, such as the historical time within which a science develops, that arise from society at large.

[14] R. W. Brown, "Chester Hamlin Werkman, 1893 – 1962," *Biog. Mem. Nat. Acad. Sci., 44* (1974), 335.

[15] Official publication, Iowa State College of Agricultural and Mechanical Arts, "The Graduate College," Annual Courses, Summer Quarter 1932, p. 5.

[16] Kluyver, Archives, Technical University of Delft, Delft, The Netherlands.

Harland Wood was born in Delvan, Minnesota, on September 2, 1907, and lived much of his early life in nearby Mankato. His upbringing was typical of most middle-class, midwestern families of the early twentieth century, except perhaps in two respects. The Wood family had six children, all of whom completed postgraduate education and had successful professional careers – a remarkable family achievement, given the economic turmoil of the times. The second noteworthy aspect of Wood's early life was his marriage to Mildred Davis at the start of their college junior year. Although the marriage required and obtained the college president's approval, September of 1929 would not seem to have been the most auspicious time to begin a marriage that was to last for more than sixty years. In high school, Wood's career interests had been in medicine, but for a variety of reasons he decided to pursue a career in chemistry and completed an undergraduate degree in chemistry at Macalester College in 1931. Werkman then offered him a fellowship to pursue graduate study in bacteriology at Iowa State.[17]

Heterotrophic CO_2-Fixation

"Wood-Werkman Reaction" is biochemical parlance for the initial observation that certain members of the bacterial genus *Propionibacterium* could convert, or fix, CO_2 into cellular material. Initially, the reaction could be written in schematic fashion as follows:

$$n\,CO_2 + n\,H_2O \Rightarrow C_n(H_2O)_n \qquad (1)^{18}$$

In a rapid series of experiments, this reaction was refined first to:

$$CO_2 + C_3\text{-compound} \Rightarrow \text{Succinic acid } (C_4H_6O_4) \qquad (2a)$$

then:

$$CO2 + \text{Pyruvic acid } (C_3H_4O_3) \Rightarrow \text{Succinic acid} \qquad (2b)$$

and ultimately stated as:

$$CO_2 + \text{Pyruvic acid} \Rightarrow \text{Oxaloacetic acid } (C_4H_4O_5) \qquad (2c)$$

[17] R. Singleton, Jr., "Harland Goff Wood: An American Biochemist," in *Comprehensive Biochemistry: History of Biochemistry*, vol. 40, ed. G. Semenza and R. Jaenicke (Amsterdam: Elsevier Science, in press).

[18] In stating the reaction in this fashion, I am taking some liberties with the initial report by Wood and Werkman. In their paper, they speculated about the nature of the various reactants and products involved in the reaction. Reaction 1 is an attempt to summarize the basic factual evidence of their report.

Reaction 2c was first referred to as "the Wood and Werkman reaction" by E. S. G. Barron in 1943,[19] and the name was used in biochemistry textbooks and the biochemical literature for many years.

When first reported in 1936, this process was startling and contrary to accepted biochemical dogma, which held that CO_2-fixation was unique to plants and a few unusual autotrophic bacteria.[20] Because propionic acid bacteria are typical heterotrophic microorganisms, the idea that they could fix CO_2 was greeted with skepticism. C. B. Niel gave a somewhat generous appraisal of Wood and Werkman's initial report when he stated, "The published results cannot, however, be considered conclusive, although the data do seem to favor their claim."[21] A less generous, but probably more typical, reaction was one observed by Wood himself as a postdoctoral fellow at Wisconsin. Wood commented to W. H. Peterson, who was reviewing a paper on citrate formation in molds, that the synthesis reported could be explained if the organisms fixed CO_2; Peterson dismissed the suggestion with the reply, "You can explain anything if you assume that."[22] Thus, for chemists and biologiests during the early third of this century, the concept that nonphotosynthetic or nonautotrophic organisms could fix CO_2 was not only an alien idea but also an idea outside their scientific worldview. In addition to the fact that notions of heterotrophic CO_2-fixation were contrary to the accepted biochemical paradigm, or what Kitcher calls "consensus practice",[23] there also were good experimental reasons to question the validity of Wood and Werkman's initial claim.

H. G. Wood, the Graduate Student

In 1931, Wood began graduate work in Werkman's laboratory at Iowa State. His thesis research was designed to resolve a controversy about the origin of succinic acid when propionic acid bacteria were grown on glucose. These heterotrophic bacteria ferment glucose to propionate, acetate, and CO_2, with

[19] E. S. G. Barron, 'Mechanisms of Carbohydrate Metabolism: An Essay on Comparative Biochemistry," in *Advances in Enzymology*, vol. 3, ed. F. F. Nord and C. H. Werkman (New York: Interscience, 1943), p. 169.

[20] M. Florkin, "CO_2 Fixation in Heterotrophs. Gluconeogenesis," in *A History of Biochemistry*, pt. 5, vol. 33a of *Comprehensive Biochemistry*, ed. M. Florkin and E. H. Stotz (Amsterdam: Elsevier Scientific Publishing, 1979), pp. 109–140; C. H. Werkman and H. G. Wood, "Heterotrophic Assimilation of Carbon Dioxide," in *Advances in Enzymology*, vol. 2, ed. F. F. Nord and C. H. Werkman (New York: Interscience, 1942), pp. 135–182; C. H. Werkman and H. G. Wood, "On the Metabolism of Bacteria," *Bot. Rev.*, *8* (1942), 1–68.

[21] C. B. van Niel, "The Biochemistry of Bacteria," *Ann. Rev. Biochem.*, *6* (1937), 608.

[22] H. G. Wood, "My Life and Carbon Dioxide Fixation," in *The Molecular Basis of Biological Transport*, ed. J. F. Woessner, Jr., and F. Huijing (New York: Academic Press, 1972), p. 7.

[23] Kitcher, *Advancement of Science* (above, n. 5), p. 31.

occasional production of other organic acids, such as succinate. Wood's basic experimental approach is called a fermentation balance: in this technique, an organism is grown on a known amount of a carbon source, such as glucose; when growth ceases, or at intermediate stages, the fermentation products are quantitatively analyzed. Based on the product ratios observed, it is possible to speculate about the metabolic processes active in the organism.[24] Wood noted the function, as well as the limits, of the technique in his Ph.D. thesis:

> Assuming satisfactory carbon and oxidation and reduction balances are obtained, it is evident that a scheme can be devised which will satisfy the requirements of the data. This, however, does not prove the scheme correct, for the intermediate mechanism could be in error and yet satisfy the observed quantities of end products. However if the scheme utilizes intermediate compounds which have been identified then it may be considered experimentally well established for it checks all facts relative to the fermentation mechanism.[25]

The comment illustrates two important experimental controls. First, to be consistent with the principle of conservation of mass, the product atomic composition had to equal the atomic composition of the growth substrate; thus, if an organism utilized 100 mmoles of glucose ($C_6H_{12}O_6$), the fermentation products needed to contain 600 mmoles of carbon, 1,200 mmoles of hydrogen, and 600 mmoles of oxygen. The second experimental control for a fermentation balance was grounded in a fundamental theory of oxidation-reduction chemistry – namely, that the sum of all oxidation reactions in a process must be balanced by equal and concomitant reduction reactions.

By the mid-1930s, Wood had essentially clarified his thesis problem, the origin of succinate from glucose during the growth of propionic acid bacteria. As he later reflected, he then began, "without any specific reason," a series of growth experiments in which glucose was replaced with glycerol.[26] The data from these experiments, summarized in Table 1, are important to understanding both the relationship between Wood and his mentor, and their individual scientific styles.

Several observations about these glycerol growth experiments are noteworthy. First, in some cultures, the amount of CO_2 recovered during the fermentation is markedly less than the amount of CO_2 introduced as the

[24] For further information on the fermentation balance technique, see A. C. Neish, *Analytical Methods for Bacterial Fermentations*, 2nd ed. (Report No. 46-8-3) (Saskatoon: National Research Council of Canada, 1952).

[25] H. G. Wood, "The Physiology of the Propionic Acid Bacteria," Ph.D. diss., Iowa State College, 1934, p. 100.

[26] H. G. Wood, "Then and Now," *Ann. Rev. Biochem., 54* (1985), 7.

Table 1. Fermentation products of *Propionibacter* cultures growth on glycerol.

Culture number	Products per 100 mmoles of fermented glycerol (mmoles)			CO_2 per 100 mmoles of fermented glycerol (mmoles)
	Propionate	Succinate	Acetate	
11W	89.3	3.9	2.6	–1.1[a]
15W	78.4	7.8	5.8	–12.3
34W	59.3	34.5	2.0	–43.2
49W	55.8	42.1	2.9	–37.7
52W	78.4	8.7	5.9	–20.0

Source: Data from H. G. Wood and C. H. Werkman, "The Utilization of CO_2 in the Dissimilation of Glycerol by the Propionic Acid Bacteria," *Biochem. J., 30* (1936), 50.
[a] The minus sign indicates that CO_2 was consumed during the fermentation process.

calcium carbonate buffer. Second, in strains that produced succinate, the amount of carbon in propionate and succinate – the major fermentation products – is greater than that in the glycerol present at the beginning of the experiment. These two observations were significant because they contradicted the first fermentation balance control – that is, the amount of carbon recovered after the fermentation did not equal the amount of carbon introduced at the beginning of the experiment. Third, in addition to propionate production, some strains produced a significant amount of succinate. This observation was equally important, because succinate is more oxidized than the growth substrate, glycerol – thus, in order for the oxidation and reduction reactions to balance, the organism also needed to produce a product more reduced than glycerol. Finally, the data are highly variable from one strain of *Propionibacterium* to another. Succinate and propionate production are roughly equivalent in strain 49W, in the other strains, however, the ratio of propionate to succinate varies from almost twofold to over twentyfold. Furthermore, CO_2 utilization is significantly high (relative to propionate production) only in strains 49W and 34W.

Wood wanted to discuss these experiments in his Ph.D. thesis, which was near completion.[27] The difficulty was explaining the anomalous fermentation balances. That he believed the balances needed explanation reflects a research style that characterized the rest of his career – a style often distinguished by the tenacious pursuit of "hunches" about the meaning of data. For example, a less determined investigator might easily have concluded that the high carbon recovery in cultures 49W and 34W arose from experimental error,

[27] J. J. Bohning, "Harland G. Wood," unpub. interview, Beckman Center for the History of Chemistry, 1990, p. 11; Wood, "My Life" (above, n. 22), p. 5; Wood, "Then and Now" (above, n. 26), p. 8.

in light of the low recoveries in cultures 11W and 15W. When faced with such anomalous results, many investigators would reasonably assume that the experiment had been incorrectly set up and discard the data as erroneous.

Wood was convinced, however, that the experiments had been properly conducted. He apparently had not focused on the total carbon recovery, but rather was concerned with two facts: in some cultures, he could not account for all of the CO_2 originally added as $CaCO_3$; furthermore, the ratio of oxidation processes was not always consistent with the reduction processes. These points, coupled with the significant production of succinate by some cultures (which distorted the oxidation/reduction ratio), convinced Wood that there was something unusual about the way these organisms were metabolizing glycerol. Therefore, in his mind, the glycerol experiments required explanation.

Later, Wood stated: "The possibility that CO_2 might be utilized . . . never entered my mind,"[28] because the intellectual mind-set at the time resisted notions that nonphotosynthetic or nonautotrophic organisms could fix CO_2. While writing his thesis, however, he was suddenly struck by the idea that "if the CO_2 is reduced, it could be the reduced product and this reduction would permit the formation of the succinate"; he then quickly "calculated the oxidation reduction balances on the basis that the missing CO_2 had been reduced. The balances were *beautiful* when the reduced CO_2 was included."[29] As seen in Table 2, the hypothesis of CO_2-fixation would simultaneously explain both the carbon balance and the oxidation reduction ratio for some of the cultures.

Despite the fact that carbon recovery *and* oxidation/reduction balance are essential controls for fermentation balances, it is clear that for Wood, carbon recovery was secondary to oxidation/reduction balance.[30] Nevertheless, a disinterested observer of the data in Table 2 might note that the balance seems to be *beautiful* only for Culture 49W; it is perhaps marginally *pretty* for Culture 11W; and it is not really all that interesting for the other three cultures. In later years the shakiness of the data may have occurred to Wood, although the rarely commented on it. In later papers reflecting on this experiment,

[28] Wood, "My Life" (above, n. 22), p. 5. This claim by Wood seems open to question. During this time, the Werkman laboratory was in correspondence with A. J. Kluyver and C. B. van Niel, both of whom were extensively thinking and writing about photosynthesis and CO_2-fixation. Indeed, van Niel formulated a major concept of photosynthesis that guided investigators in the field for many years. Both Kluyver and van Niel visited the Werkman laboratory during Wood's graduate study. Thus, there must have been a great deal of laboratory discussion and speculation about CO_2-fixation, which may well have "primed" Wood to think about such a possibility to explain his anomalous data.

[29] Wood, "My Life" (above, n. 22), p. 5 (emphasis added).

[30] Bohning, "Harland G. Wood" (above, n. 27), p. 11.

Table 2. Carbon and oxidation/reduction balances of data from Table 1, calculated on the basis of CO_2-fixation or nonfixation.

	Carbon balance (%)		Oxidation/reduction	
Culture number	CO_2 not included	CO_2 included	CO_2 not included	CO_2 included
11W	96.8	96.5	1.162	1.135
15W	92.6	89.1	1.376	1.047
34W	106.0	93.1	2.270	0.925
49W	114.0	101.2	2.550	1.081
52W	101.0	94.6	1.386	0.918

Source: Data from H. G. Wood and C. H. Werkman, "The Utilization of CO_2 in the Dissimilation of Glycerol by the Propionic Acid Bacteria," *Biochem. J., 30* (1936), 50.

he generally cited data only for those cultures that were consistent with the hypothesis of CO_2-fixation,[31] or he quoted data from a 1938 paper where the experiment had been repeated under cleaner and more rigorous conditions. One of his few direct comments on the high variability of these data was a reflection that the metabolism of the propionic acid bacteria was highly variable from one strain to another.[32]

After formulating an innovative hypothesis for his anomalous data, Wood "rushed to the Bacteriology Department to [tell Werkman that] the thesis would have to be rewritten completely."[33] Wood believed that his thesis explanation of glucose utilization needed reinterpretation in light of this new metabolic insight. Werkman apparently listened patiently and, according to Wood, replied: "The thesis is all typed except the bibliography, we don't want to write it again. Let's let the thesis go as it is and we'll take care of this question of CO_2 fixation later."[34]

Werkman's true reactions to these data are not clear. Wood presented the results at the 1935 meeting of the North Central Branch of the Society of American Bacteriologists (now American Society for Microbiology).[35] As Wood was presenting the paper, Werkman allegedly agreed with people sitting around him that he "didn't believe a word of the data."[36] However, he had

[31] See, for example, Table 1 in Wood, "My Life" (above, n. 22), p. 6.

[32] H. G. Wood, "Trailing the Propionic Acid Bacteria," in *Reflection on Biochemistry in Honor of Severo Ochoa*, ed. A. Kornberg, B. L. Horecker, L. Cornudella, and J. Oro (New York: Pergamon Press, 1976), pp. 105–115.

[33] Wood, "My Life" (above, n. 22), p. 5.

[34] Ibid., p. 6.

[35] H. G. Wood and C. H. Werkman, "The Utilization of CO_2 by the Propionic Acid Bacteria in the Dissimilation of Glycerol," *J. Bacter., 30* (1935), 332.

[36] Wood, "Then and Now" (above, n. 26), p. 8.

sufficient confidence in the work to coauthor a paper that Wood wrote (while a postdoctoral fellow at Wisconsin) for submission to *Biochemical Journal*.[37]

Regardless of Werkman's evaluation of the CO_2-fixation data, during Wood's time as a graduate student in his laboratory (1931–1935) they produced sufficient data for thirteen major publications. This rate of publication is even more remarkable in light of the fact that for most of this time Wood's appointment was a nine-month contract. He was married and had one child; financial considerations were important.[38] Consequently he spent several summers during his graduate career working in the family business in Mankato, Minnesota, and was not able to work in the laboratory.

H. G. Wood, the Postdoctoral Associate

Wood spent in 1935/36 academic year as a National Research Council (NRC) Postdoctoral Fellow working with E. L. Tatum in William Peterson's laboratory at the University of Wisconsin, focusing on the vitamin requirements for efficient growth of propionic acid bacteria. It was also a productive year in which Wood wrote several papers published with Werkman (including the pivotal *Biochemical Journal* paper), and completed experimental work for three papers that he published with Tatum and Peterson. Thus, by the end of 1936 Wood was coauthor (either published or in press) of more than sixteen full papers produced in about six years.

Animosity apparently developed between the former student and his mentor, perhaps elicited by Werkman's resistance to accepting the heterotrophic CO_2-fixation hypothesis. Wood believed that his doctoral thesis was incomplete without the CO_2-fixation data.[39] From his perspective, the thesis results were wrong and needed reinterpretation in light of the organism's capability for CO_2-fixation, and he apparently resented Werkman's somewhat cavalier rejection of his argument. If Werkman's comment on the validity of the data presented at the Society of American Bacteriologists meeting is accurate, the animosity may well have been justified.

Wood had planned to spend the second year of his NRC Fellowship with Otto Meyerhof, whose laboratory was a leading center of metabolic inquiry and whose work was directly influencing Wood's research work.[40] Thus,

[37] H. G. Wood and C. H. Werkman. "The Utilization of CO_2 in the Dissimilation of Glycerol by the Propionic Acid Bacteria," *Biochem. J., 30* (1936), 48–53.

[38] For example, Wood's widow notes that the $50 monthly income the family received, they spent almost $34 on rent; to make financial ends meet, Wood tended the furnace of the apartment building in which they lived: Interview with Mildred D. Wood, Cleveland, Ohio, December 29, 1993.

[39] Wood, "My Life" (above, n. 22), p. 6.

[40] Wood, "Then and Now" (above, n. 26), p. 9.

it may seem mildly surprising that in the fall of 1936 Wood returned to Iowa State, where he held a series of research positions – ranging from research assistant, to research associate, to research assistant professor – in the Bacteriology Section of the Agricultural Experiment Station. From 1942 until he left Iowa State, he held a joint appointment (1/3 time) as assistant professor in the Bacteriology Department.[41]

If the animosity between Wood and Werkman was real, it seems reasonable to ask why Wood returned to Werkman's laboratory; however, the historical record is ambiguous on this question. Wood commented, "I returned to Iowa State University following the year of postdoctoral work at Wisconsin and continued the work on fixation of CO_2."[42] Two hypotheses seem possibly to explain his return to Iowa; indeed, both explanations most likely played pivotal roles. First, in 1936 the economic depression shaped many American lives. Despite Wood's significant publication record and promise as an independent researcher, it may be that academic positions were unavailable. Wood lent credence to this hypothesis when he stated: "Professor Werkman offered me a position, . . . *Jobs were few and far between* so I accepted Werkman's offer."[43]

An alternative hypotheses for Wood's return to Iowa, and one more relevant to our understanding of the mentor-student relationship, is that Werkman would not allow Wood to work on the CO_2-fixation problem in another laboratory, especially one actively pursuing research on metabolic processes. This hypothesis suggests that Werkman wanted to maintain control of the research despite his alleged skepticism about its correctness – and there is partial support for this notion. In an interview, Wood elaborated on his desire to spend the second year of his NRC fellowship in Meyerhof's laboratory: he commented that Werkman insisted that if he did not return to Iowa that year (1936) the offer of a position would be withdrawn, and he briefly hinted at Werkman's concern over losing control of the CO_2-fixation problem if Wood were to move to a more powerful laboratory such as Meyerhof's.[44]

At any rate, Wood returned to Werkman's laboratory, where they began an extensive collaborative program that focused on CO_2-fixation. It appears to have been an unusual collaboration in that Werkman was intellectually distant from the research effort but maintained essential financial support from various grants and contract sources, whereas Wood provided the intellectual and scientific motivation for the research. The relationship also illustrates

[41] All of Wood's appointments are documented in Annual Budgets for Iowa State College, State of Iowa Board of Regents Minutes, Archives, Iowa State University, Ames, Iowa.

[42] Wood, "My Life" (above, n. 22), p. 7.

[43] Wood, "Then and Now" (above, n. 26), p. 9 (emphasis added).

[44] Bohning, "Harland G. Wood" (above, n. 27), p. 22.

that people can often work together even though they may not be very happy with each other; indeed, often they must collaborate whether they like each other or not.[45] Nevertheless, it was a collaboration that Wood described as "enjoyable and productive."[46] Perhaps *enjoyable* may have been a bit disingenuous in Wood's description, but the time in Werkman's laboratory was certainty *productive*. During the seven years from 1936 to 1943, they generated sufficient data to coauthor twenty-nine full papers. It is significant that Wood had no single-author papers during this time, nor did he coauthor any papers without Werkman's name on them (with the exception of the three papers from Tatum's laboratory). An analysis of Werkman's publications demonstrates that during their total interaction, Wood coauthored forty-two papers with Werkman, or about 13 percent of Werkman's total publication record (see also Table 3).[47]

Shortly after his return to Iowa State, Wood repeated the fermentation balance experiments described previously, but with two important differences. First, he designed a fermentation apparatus in which gas volumes and pressures could be kept constant and periodically measured.[48] The apparatus design and function were based on Warburg's manometric techniques, which had then gained widespread popularity, and allowed rate measurements not possible in the static fermentations.[49] Wood himself both designed and constructed critical components of the apparatus, including some fairly sophisticated glass-blowing. The apparatus also allowed samples to be removed periodically during the fermentation, for substrate and product analysis.[50] Second, he repeated the previous static fermentations, this time taking precautions to ensure that atmospheric CO_2 could not enter the fermentation

[45] I thank David Hull for bringing this point to my attention.

[46] Wood, "Then and Now" (above, n. 26), p. 13.

[47] All analysis of Werkman's publications is based on the extensive bibliography included in Brown, "Chester Hamlin Werkman" (above, n. 14).

[48] H. G. Wood, C. A. Brewer, M. N. Mickelson, and C. H. Werkman, "A Macro-respirometer for the Study of the Anaerobic Metabolism of Microorganisms," *Enzymologia, 8* (1940), 314–317.

[49] F. L. Holmes, "Manometers, Tissue Slices, and Intermediary Metaboism," in *The Right Tools for the Job in Twentieth-Century Life Sciences: Materials, Techniques, Instruments, Models, and Work Organization,* ed. A. Clarke and J. Jujimura (Princeton: Princeton University Press, 1992), pp. 151–171.

[50] Although many scientific instruments were commercially available during this time, a hallmark of a skilled investigator was the ability to construct equipment necessary for research investigation; see Clarke and Fujimura, *Right Tools for the Job*. Like many of his contemporaries trained in chemistry, Wood was apparently a skilled glass worker. George Kalnitsky has remarked on Wood's skill at constructing the specialized flasks necessary for the modified Warburg apparatus. Kalnitsky further noted that Wood was one of the few people in the laboratory who could make the glass bulbs necessary for the construction of glass electrodes of pH measurement (G. Kalnitsky, letter to the author, October 1993).

flask – an essential control absent in the previous experiments. He also used a more reliable method of succinate analysis in order to ensure greater precision and accuracy in the data for succinate production during the fermentation. In these experiments the carbon recoveries and oxidation/reduction balances were uniformly closer to expected values, when CO_2-utilization is included. The stoichiometric relationship between the CO_2 utilized and the succinate produced was also more readily apparent.[51]

That CO_2 reacts with a three-carbon compound to form either a precursor of succinate or succinate itself was further supported using Carl Neuberg's bisulfite trapping technique, which caused pyruvate to accumulate in the fermentation mixture.[52] This observation was compelling evidence that pyruvate was a metabolic intermediate in the genus *Propionibacterium* and suggested that it was the three-carbon acceptor for CO_2. Thus, in 1938 Wood and Werkman proposed that CO_2-fixation occurred via the following process in glycerol utilization by the propionic acid bacteria:

$$\text{Pyruvate} + CO_2 \Rightarrow C_4\text{-compound} \tag{3}$$

Furthermore, because of the approximately equimolar ratio between the CO_2 fixed and the succinate produced, they proposed that the C_4-compound was most likely succinate, or a precursor compounds.[53]

A powerful test of any scientific hypothesis is its ability to answer questions not directly related to the immediate phenomena. In the 1938 paper, Wood used the concept of CO_2-fixation to explain an observation of A. I. Virtanen and A. Karström that the propionic acid bacteria produced equimolar amounts of succinate and acetate from glucose when grown in the presence of toluene.[54] Virtanen and Karström claimed that the reaction occurred by directly splitting glucose (a C_6 compound) into succinate (a C_4 compound) and acetate (a C_2 compound). Wood first noted the logical difficulty, based on the then-most-accepted metabolic reactions, in the Virtanen and Karström proposal: metabolic concepts formulated by Gustav Embden, Meyerhof, and Jakub Karol Parnas were establishing the principle that glucose was split into two C_3 compounds. Wood then noted that this difficulty was easily explained

[51] H. G. Wood and C. H. Werkman, "The Utilization of CO_2 by the Propionic Acid Bacteria," *Biochem. J., 32* (1938), 1262–1271.

[52] Bisulfite reacts with carbonyl groups in organic compounds to form stable complexes. If such compounds are intermediates in a metabolic pathway, the addition of bisulfite will inhibit the pathway and cause accumulation of the carbonyl-containing compound. Neuberg used the technique to great advantage in sorting out metabolic intermediates in yeast fermentations.

[53] Wood and Werkman, "Utilization of CO_2" (above, n. 51); H. G. Wood, R. W. Stone, and C. H. Werkman, "The Intermediate Metabolism of the Propionic Acid Bacteria," *Biochem. J., 31* (1937), 349–359.

[54] A. I. Virtanen and A. Karström, "Über die Propionsäuregärung, III," *Acta Chem. Fennica*, Ser. B, *7* (1931), 17.

by postulating that the C_6 compound was split into two C_3 compounds, presumably pyruvate, by reactions already well understood; one of the C_3 intermediates was decarboxylated to acetate (a C_2 compound), and the other carboxylated to succinate (a C_4 compound). Thus, if the hypothesis of CO_2-fixation was correct, it would help explain Virtanen and Karström's unusual 1931 observations. By expanding the explanatory power of the hypothesis, Wood provided additional credence for its validity.

Contemporaneous work from the laboratories of Embden, Meyerhof, and Parnas in the late 1930s began to clarify the fermentation of glucose and to demonstrate the role of phosphorylated intermediates in that process.[55] Drawing on inferences from the Embden-Meyerhof-Parnas pathway, and on the observation that sodium fluoride inhibited CO_2-fixation with a concomitant and stoichiometric reduction in the amount of succinate produced, Wood and Werkman concluded that succinate was the most likely C_4-compound in Reaction 3.[56] The 1940 papers also demonstrated a requirement for phosphate in the reaction and speculated that succinate arose from the carboxylation of phosphoenolpyruvate to yield oxaloacetate, which was reduced to succinate in a subsequent reaction. The later suggestion was not confirmed until the discovery, by Patrick Siu in the early 1960s, of the enzyme phosphoenolpyruvate carboxytransphosphorylase.[57]

Expansion of the Research Program

By late 1939, Wood and Werkman had firmly established the basic chemistry of heterotrophic CO_2-fixation using techniques no more sophisticated than simple fermentation balances combined with selective metabolic inhibitors.[58] At this stage, the research program began to expand via seemingly unusual twists and turns, which were not always scientific. In 1939, Wood attended the International Congress of Microbiology in New York and heard about ^{11}C, which was produced in the Berkeley cycltron, as a radioactive tracer of metabolic processes. It was immediately obvious that using $^{11}CO_2$ as a

[55] W. Bechtel, "Biochemistry: A Cross-disciplinary Endeavor That Discovered a Distinctive Domain," in *Integrating Scientific Disciplines*, ed. idem (Dordrecht: Martinus Nijhoff, 1986), pp. 77–100; idem, "The Nature of Scientific Integration," in ibid., pp. 3–51.

[56] H. G. Wood and C. H. Werkman, "The Fixation of CO_2 by Cell Suspensions of *Propionibacterium pentesaceum*," *Biochem. J., 34* (1940), 7–14; idem, "The Relationship of Bacterial Utilization of CO_2 to Succinic Acid Formation," ibid., pp. 129–138.

[57] P. M. L. Siu, H. G. Wood, and R. L. Stjernholm, "Fixation of CO_2 by Phosphoenolpyruvic Carboxytransphosphorylase," *J. Biol. Chem., 236* (1961), PC21–22; P. M. L. Siu and H. G. Wood, "Phosphoenolpyruvic Carboxytransphosphorylase, a CO_2-Fixing Enzyme from Propionic Acid Bacteria," *J. Biol. Chem., 237* (1962), 3044–3051.

[58] For excellent contemporary summaries of this evidence, see Werkman and Wood, "Heterotrophic Assimilation" and "On the Metabolism of Bacteria" (both in n. 20, above).

tracer in the glycerol fermentation would provide powerful evidence for the validity of the heterotrophic CO_2-fixation hypothesis. The experiment would have the further advantage of identifying unequivocally the carbon-fixation product (the C_4-compound in Reaction 2c). There were two problems with the potential experiment, only one of which was technical: the half-life of ^{11}C is 20.5 minutes; thus, the entire experiment would have to be completed in fewer than six hours to obtain useful data. The second problem ultimately involved in sociology of science: the only source of ^{11}C was at the end of the Berkeley cyclotron; because of the short half-life of the isotope, Wood would have to travel to Berkeley to do the experiment.

Wood returned to Ames from the congress and immediately began to design the experiment and run it under sham conditions. He demonstrated that he could carry out the fermentation and isolate the appropriate products in sufficient time for the experiment to demonstrate $^{11}CO_2$-fixation. He described his reaction as follows: "I was elated, and told Professor Werkman that I would drive to California during the summer vacation to conduct the experiment. To my astonishment, Professor Werkman said, 'no, you can't go.' "[59] Wood saw this experimental approach as a clear way to directly and unequivocally confirm the heterotrophic CO_2-fixation hypothesis.[60] Furthermore, his commitment to the research inquiry was such that he was willing to spend his own money for travel to Berkeley. Wood commented on numerous occasions that he could never understand Werkman's hesitancy to pursue the research inquiry by collaboration with the Berkeley isotope group. He speculated that had Werkman done so, he might have lost control of the problem, because the only source of ^{11}C was in Berkeley.[61]

Wood's speculation regarding Werkman's need for control is reasonable; however, the depth of Werkman's intellectual commitment to the hypothesis of heterotrophic CO_2-fixation, *at the time*, is not clear. In a comprehensive, insightful, and elegantly written review of carbohydrate metabolism, Werkman mentions work on CO_2-fixation, from *his own laboratory*, only twice in forty pages. One reference is almost dismissive: "The utilization of CO_2 by the propionic acid bacteria . . . *may* represent a vestige of autotrophism in

[59] Wood, "My Life" (above, n. 22), p. 8.

[60] Wood's prescience of the power of isotopic tracers was confirmed the following year when Evans and Slotin used $^{11}CO_2$ to demonstrate assimilation in pigeon-liver preparations: E. A. Evans, Jr., and L. Slotin, "The Utilization of Carbon Dioxide in the Synthesis of α-ketoglutaric Acid," *J. Biol. Chem.*, *136* (1940), 301–302. Thus, the first *direct* experimental proof for heterotrophic CO_2-fixation did not come from the Wood-Werkman laboratory.

[61] Bohning, "Harland G. Wood" (above, n. 27), p. 12; Wood, "My Life" (above, n. 22), p. 7; Wood, "Then and Now" (above, n. 26), p. 8.

otherwise heterotrophic organisms."[62] Although later in the review he alludes to the possibility that heterotrophic CO_2-fixation may be involved in photosynthesis, the suggestion again is brief and indirect. It seems strange that a scientist would refer to major and revolutionary work emerging from his own laboratory in such oblique and tentative language. In David Hull's view of science, successful scientists must become advocates for their new ideas,[63] and review papers provide opportunities for individuals to advance the work of their own laboratories in powerful ways. It is thus somewhat surprising that Werkman did not more forcefully emphasize the notion of heterotrophic CO_2-fixation in his review, if he indeed had a major intellectual commitment to the idea. His somewhat causal treatment of the concept, in an otherwise extremely well written paper, suggests that the true intellectual commitment to the hypothesis was Wood's and not his mentor's. Thus, Werkman's motives for not permitting Wood to go to Berkeley may have been mixed: he wanted to retain full control over the research, as Wood suggested, and he may also have not wanted Wood to be away from the Ames laboratory for a protracted period of time, doing work that might ultimately be unproductive.

During a summer vacation at his parents' home near Mankato, Minnesota, Wood told his brother, Earl, about the research impasse with Werkman. Earl Wood was then completing his M.D.-Ph.D. in physiology at the University of Minnesota and was familiar with the work of A. O. Nier in the Physics Department at Minnesota. Nier had developed techniques for isolating and measuring the heavy (nonradioactive) carbon isotope ^{13}C. Earl suggested that perhaps $^{13}CO_2$ could be used as a tracer in much the same fashion as Wood had planned to use $^{11}CO_2$. Wood immediately contacted Nier, and there "then began a very useful and exciting collaboration and *with Professor Werkman's blessing*."[64] The phrase "useful and exciting collaboration" seems a most remarkable understatement. During slightly more than a year, the Werkman/Wood and Nier laboratories produced nine major papers in which they confirmed the hypothesis of heterotrophic CO_2-fixation and demonstrated that $^{13}CO_2$ was incorporated into the carboxyl group of succinate. Furthermore, the extensive collaboration helped clarify a number of fundamental metabolic questions regarding intermediates of the citric acid cycle.

The work on the citric acid cycle further illustrates the complex relationship between Wood and Werkman. Wood was convinced that CO_2-fixation was not an exclusive activity of the propionic acid bacteria, but rather a universal metabolic process. Commenting on Krebs's observation that citrate synthesis

[62] C. H. Werkman, "Bacterial Dissimilation of Carbohydrates," *Bacter. Rev., 3* (1939), 190 (emphasis added).

[63] Hull, *Science as a Process* (above, n. 2), p. 361.

[64] Wood, "My Life" (above, n. 22), p. 8.

involved oxaloacetate and some unknown compound, Wood and Werkman noted in their 1938 paper that "it is possible that this synthesis involves carbon dioxide."[65] Later, Wood stated: "I was convinced that carbon dioxide fixation would not be appreciated until it could be shown to occur in animals, and was continually prodding Professor Werkman to permit me to do an experiment with animals."[66] Apparently, Werkman strongly resisted such experiments because of the constraints of disciplinary and departmental boundaries. His department was, after all, a *bacteriology* department – and consequently, from Werkman's perspective, the focus of their research should remain on microorganisms.

Werkman's resistance to working with nonmicrobial organisms may seem surprising, and perhaps illustrates a way in which scientists can become entrapped by self-imposed disciplinary boundaries. The resistance is surprising because Werkman's perspective on bacteriology was significantly multidisciplinary. Indeed, during the early 1930s he became a leader of the movement that approached the study of microbiology from physical and chemical perspectives. According to Brown, Werkman was among the pioneering group of scientists who insisted that chemical principles could best be used to understand microorganisms. Brown notes that Werkman "viewed microorganisms as intriguing systems of enzymes capable of a multiplicity of chemical transformations, but with relative similarity in their basic biochemical behavior . . . he was most at home with chemists."[67] Given this eagerness to cross the disciplinary boundaries between chemistry and biology, one has to wonder at Werkman's hesitancy about applying the metabolic principles of microorganisms to other life forms.

Eventually, Wood was able to wear down Werkman's resistance – in large measure, because of external pressures. In 1940, evidence began to appear suggesting a role for CO_2-fixation in pigeon-tissue citrate metabolism.[68] Wood "rushed to show Professor Werkman" the data.[69] Werkman relented, and soon the laboratory was doing experiments involving $^{13}CO_2$-fixation and minced pigeon liver. Wood considers portions of this work to be some of his most important contributions to biochemistry, for it ultimately led to clarification of Krebs's assertions about carbon flow in the citric acid cycle.

Although the collaboration with Nier was successful, it became increasingly clear to Wood that the Iowa group needed to develop their own ability to work with ^{13}C. Thus, they approached Nier about the feasibility of assembling a

[65] Wood and Werkman, "Utilization of CO_2" (above, n. 51), p. 1269.
[66] Wood, "My Life" (above, n. 22), p. 8.
[67] Brown, "Chester Hamlin Werkman" (above, n. 14), p. 336.
[68] Evans, Slotin, "Utilization of Carbon Dioxide" (above, n. 60).
[69] Wood, "My Life" (above, n. 22), p. 11.

thermodiffusion column (to isolate the heavy isotope of carbon) and a mass spectrometer (needed to measure levels of $^{13}CO_2$) at Ames. Nier agreed, and facilitated some equipment construction at Minnesota; other components were constructed in shops at Iowa State, as well as in the Werkman laboratory. Assembly of the equipment was a collaborative effort involving most of the graduate students then in the Werkman laboratory. When the project was completed in 1942, it illustrated A. E. Clarke and J. H. Fujimura's notion of "co-construction of tools, jobs, and rightness."[70] The facility brought together in one location a highly sophisticated experimental tool with a group of skilled investigators who had important questions the tool could be used to answer; it made the Werkman laboratory at Iowa State one of the few places in the country with a capability to study microbial physiology utilizing isotopically labeled compounds. The Werkman group was also amazingly skilled and talented: it include three members who eventually were elected to the National Academy of Sciences (Wood, Merton Utter, and Lester Krampitz), in addition to Werkman himself.

It is apparent that Werkman had developed a full intellectual commitment to the heterotrophic CO_2-fixation hypothesis by this time. In 1942, he and Wood coauthored two reviews, both of which focused extensively on the wide-reaching implications of the "Wood and Werkman reaction" for metabolic processes.[71] In the *Botanical Review* paper, for example, they built a strong argument for the relatedness of bacteria to plants, and then extended this argument to suggest that heterotrophic CO_2-fixation may represent some vestiges of the "dark reactions" of photosynthetic CO_2-fixation. In a lecture prepared for the Iowa State Chapter of Sigma Xi, Werkman was explicit about the possible connection between heterotrophic and photosynthetic CO_2-fixation: "The process of photosynthesis from this point on [after the photoreactions involving chlorophyll] is a dark reaction and is concerned with the utilization of carbon dioxide to form carbohydrate. . . . We would like to suggest that the mechanism of carbon dioxide utilization as worked out on this Campus [i.e., the Wood-Werkman reaction] would start the synthesis."[72]

Shortly after helping assemble this superb research facility, Wood left Werkman's laboratory during the summer of 1943 to become an associate professor in the Physiology Department at the University of Minnesota. Later he commented, in a statement that verges on irony, "my fine collaboration with

[70] A. E. Clarke and J. H. Fujimura, "What Tools? Which Jobs? Why Right?" in idem, *Right Tools for the Job* (above, n. 49), p. 7.

[71] Werkman and Wood, "Heterotrophic Assimilation" and "Metabolism of Bacteria" (both above, n. 20).

[72] Unpub. ms labeled "Rough draft: C. H. Werkman talk to Sigma Xi. 1942," private papers of Robert T. Werkman.

Professor Werkman was no longer as friendly as it had been."[73] The comment seems ironic in two respects. As I suggested previously, the collaboration with Werkman had had tumultuous moments; nevertheless, it also had truly been "fine" in terms of research accomplishment. The Wood-Werkman reaction was fully accepted in biochemical circles. For example, H. A. Barker, who had previously been critical of the original report of heterotrophic CO_2-fixation, said in a 1941 review: "The *remarkable* results of Wood & Werkman on the utilization of carbon dioxide by propionic acid bacteria have now been *completely confirmed* and extended in several laboratories."[74] Furthermore, Wood was increasingly recognized as an independent and creative scientist, as indicated by his receipt of the Eli Lilly Award in Bacteriology in 1942.[75] This independent reputation developed despite the fact that, with the exception of the work from his NRC year, he had not published a single paper without Werkman's name on it.

A deep enmity in the relationship apparently arose over the collaboration's success. After receipt of the Lilly Award, in 1943 the Wood family decided to buy a home in Ames. When Werkman heard about the real estate purchase, he asked Wood, "Why did you do that, do you think you can stay here forever?"[76] Wood said that he was shocked by Werkman's remark, seemingly because there had been an implication that his position at Iowa State was indeed permanent. Wood apparently had turned down an associate professorship at Minnesota prior to the planned real estate purchase. There is independent corroboration for this claim of the job offer: George Kalnitsky, who was a graduate student in the laboratory, remembers Wood storming out of Werkman's office and saying that now he was "sorry he had turned down the Minnesota job offer."[77] His reason for not wanting to move from Ames was grounded in the excellent research facilities he had helped establish there; as he noted, "We had a plant unmatched anywhere else in the world."[78] The Iowa laboratory possessed both the physical ability to produce and study isotopically labeled compounds *and* the ability (equally essential) to study biological processes such as intermediary metabolism. For an inves-

[73] Wood, "My Life" (above, n. 22), p. 19.

[74] H. A. Barker, "The Chemistry and Metabolism of Bacteria," *Ann. Rev. Biochem.*, *10* (1941), 570 (emphasis added).

[75] The Eli Lilly Award, begun in 1936, is annually given by the American Society for Microbiology (ASM) to recognize young investigators (under the age of forty) who are making significant contributions to the science of microbiology. It is, perhaps, the ASM's most prestigious award. Several recipients have later won the Nobel Prize, and numerous recipients have later become members of the National Academy of Sciences.

[76] Wood, "Then and Now" (above, n. 26), p. 13.

[77] Kalnitsky letter (above, n. 50).

[78] Bohning, "Harland G. Wood" (above, n. 27), p. 22.

tigator committed to this study, the Iowa facility would be difficult to leave. It is hard to understand why Werkman allowed, apparently even forced, this obviously productive collaboration to dissolve so abruptly. Forty years later, Wood commented that he had “never quite forgiven Werkman for wrecking this opportunity for some truly excellent research and science.”[79] Although the historical record is relatively silent on the issue, two speculative motives seem reasonable.

Seen in its most charitable light, it may be that Werkman saw sufficient research potential in Wood to realize that his protégé could develop full independence only in a different environment. In this light, Werlman’s action is that of a kindly parent, pushing the fledgling from the nest to make its own way in the world. Wood eventually realized that the move was personally a fortunate one and stated, “Werkman kicked me out of a place where I probably couldn’t have gotten very far ahead.”[80]

A more malevolent perspective on Werkman’s action is that of a demanding, highly controlling individual, who was threatened by his colleague’s superior abilities. There seems little doubt that Werkman insisted on maintaining full control of the collaboration’s administrative aspects. In his 1990 interview with James Bohning, Wood made several references to such a need for control by Werkman. A key point of contention between the two men prior to the collaboration’s breakup was a request by Wood for a small amount of independent financial support and more formal access to graduate students; Werkman was unwilling to relinquish control of either.[81]

After the Breakup

Both Werkman and Wood had distinguished scientific careers that are impossible to encapsulate in a brief essay. Thus, a few brief comments must serve here to indicate the complexity of their independent work.

Werkman served as chairman of the Bacteriology Department from 1945 until 1957, when he stepped down because of ill health. He was elected to the National Academy of Sciences in 1946. It is striking that within a few years of Wood’s departure for Minnesota, other members of Werkman’s research group also left Ames; several of them later joined Wood at Western Reserve University. Although Werkman continued to publish during the years after Wood left his laboratory, the frequency of his publications diminished markedly. For example, during the twelve-year period from 1931 to 1943, the Werkman laboratory published between six and seventeen papers a year. For

[79] Wood, “Then and Now” (above, n. 26), p. 14.
[80] Bohning, “Harland G. Wood” (above, n, 27), p. 18.
[81] Ibid., pp. 18, 22.

the eight-year period from 1936 to 1943, the "three-year running average" of publications exceeded ten papers per year. After 1943, it was unusual for the laboratory to publish more than five papers a year, and the "three-year running average" varied between three and eight papers per year (the eight-paper average was in 1944).

After leaving Werkman's laboratory, Wood's career was remarkable for the volume and diversity of his research, although the thread of heterotrophic CO_2-fixation ran through much of the work. Wood left Minnesota in 1946 to head the Biochemistry Department at Western Reserve (later Case Western Reserve) University School of Medicine, where he remained (with the exception of occasional sabbatical years) until his death in 1991. Like Werkman, he was elected to the National Academy of Sciences (in 1953). As the leader of a strong basic science department, Wood was a driving force to implement Dean Joseph Wearn's integrated medical curriculum.[82] He served as departmental chairman until 1965, when he was succeed by his friend and colleagues Merton Utter. He also served as Dean of Sciences at Case Western Reserve University from 1967 to 1969.

Wood's research program in the post-Werkman years can be characterized as imaginative, evolutionary, collaborative, and highly productive. He and his colleagues created numerous techniques to assess a variety of metabolic processes, in organisms ranging from bacteria to cows. They made extensive use of ^{14}C as a tracer for various metabolic pathways when the radioactive isotope of carbon became available, and they contributed to the theoretical use of isotopes as measures of metabolic activity. Wood continued his investigations of the production of propionic acid in the genus *Propionibacterium* and eventually isolated and characterized all of the enzymes in the pathway. His clarification of the propionic acid cycle is an indication of the evolutionary nature of his research inquiry.[83] Consider that he began the investigation using techniques of fermentation balances, but that near the end of his career he was studying the molecular architecture of the enzymes involved in the pathway.[84] To say that Wood's research program was "highly productive" is to understate the case: from the time he left Werkman's laboratory until his death in 1991, he published more than 230 papers, many of which profoundly influenced biochemistry.

[82] G. Williams, *Western Reserve's Experiment in Medical Education and Its Outcome* (New York: Oxford University Press, 1980).

[83] Singleton, "Harland Goff Wood" (above, n. 17).

[84] Wood, "Trailing the Propionic Acid Bacteria" (above, n. 32).

Collaboration and Styles of Science Practice

If we agree that the extensive collaboration between Wood and Werkman is the story of a single mentor-student interaction, and thus are careful about sweeping generalizations, I believe that this case study can provide insight into the nature of modern science practice. The story clearly illuminates the different styles and approaches that individual scientists bring to science. While these styles may, in part, reflect local institutional constraints, they are also highly idiosyncratic and reflective of the participants' individual personalities. Finally, the story illustrates ways in which individual styles can affect scientific mentoring, and it thus has general implications for our understanding of scientific collaboration.

Styles of Science Practice and Student Mentoring

Many aspects of the Wood-Werkman interaction indicate that Werkman was detached from daily laboratory operation. Wood stated that "Werkman provided little direction for his lab's research projects."[85] He noted that Werkman had weekly conferences with his students, but from Wood's perspective those conferences provided little research guidance: "When I'd go up to talk to him, all I would ever hear was his problems. We'd never talk research."[86] Comments by other Werkman students support Wood's view. For example, R. W. Brown (an early graduate student and a Wood contemporary), in remarks made in a tribute to Werkman shortly after his death, observed: "I can recall only a few occasions, during my time, when he worked in the laboratory with his own hands; he had a group of enthusiastic and dedicated students who worked for him."[87] Even the physical layout of offices and laboratories may have led to an isolation of mentor from students: Werkman's office was located on the first floor of the building, and his laboratories were in the basement. It is not unreasonable to conclude that in such a laboratory situation, a bright and energetic senior person in the laboratory might become a "surrogate mentor" for other graduate students in the laboratory. This conclusion is supported by Wood's observation that "in a way I was almost running the lab towards the end."[88]

Other Werkman students support this perspective that their research supervisor was detached from close laboratory mentoring. According to Merton

[85] Wood, "Then and Now" (above, n. 26), p. 15.
[86] Bohning, "Harland G. Wood" (above, n. 27), p. 10.
[87] R. W. Brown, "A Tribute to Chester Hamlin Werkman," unpub. comments, May 18, 1963, private papers of Robert T. Werkman.
[88] Bohning, "Harland G. Wood" (above, n. 27), p. 10.

Utter's widow, his perception was that Werkman put students on problems that were extremely difficult, and then let them "sink or swim" on their own.[89] Such an environment would foster strong collegial relationships between senior and junior members of the research group. For example, Mrs. Utter suggested that this was part of the reason that Wood and Utter became such lifelong friends and research colleagues. Thus, it was not coincidental that Utter left Werkman's laboratory to join Wood at Minnesota, moved to Western Reserve when Wood became the Biochemistry chairman there, and ultimately became department chair when Wood stepped down.

George Kalnitsky further endorses this view of Werkman's detachment from the laboratory, and of other members of the laboratory as guiding his work, and confirms Wood's observations about the lack of communication at the weekly laboratory meetings:

> Werkman scheduled regular weekly research conferences with each graduate student. Mine was scheduled at 8 am. It was changed to a later hour, he told me because he saw I was in the lab by 8 am every morning anyway. At these research meetings, I presented the data I had obtained since our last meeting, he read it, asked a question or two . . . mentioned something general. . . . I don't remember that he ever made any suggestions about my research. None. None at all.[90]

From Kalnitsky's perspective, Utter and Wood both served as his research mentors. In an interview, he discussed how Wood taught him to prepare ^{13}C-labeled compounds and use the mass spectrometer to measure the isotope levels – techniques central to the development of his thesis. He also mentioned that in his writing of papers, guidance came from Utter and Wood, rather than from Werkman.[91] Thus, it is interesting that of the six papers Kalnitsky coauthored with Werkman, Utter is a coauthor on two and Wood a coauthor on one.

Although some of Werkman's students found little value in their thesis director's guidance, other former students conclude that his direction was subtle and valuable. Eric Fowler, for example, tells the story of needing an expensive isotopically labeled compound: when he approached Werkman about purchasing the compound, Werkman said that the cost was prohibitive; "he then handed me a treatise on organic synthesis in which he had marked a procedure for the synthesis of [the compound]; there was no comment." Fowler found the compound he synthesized for the experiment fully satisfactory, and the money saved allowed the laboratory to purchase new equipment

[89] Mrs. M. F. Utter, letter to the author, June 24, 1993.
[90] Kalnitsky letter (above, n. 50).
[91] Interview with G. Kalnitsky, Iowa City, July 10, 1994.

necessary for new laboratory techniques. Fowler concluded: "Dr. Werkman's actions had been subtle in the extreme; the mystery was that he knew how to stimulate confidence."[92]

Student Impact as Collaborators

The discussion thus far has considered the professional impact of scientific mentoring collaboration only indirectly; I now want to explore specifically the ways in which this particular collaboration affected the participants' scientific careers. The previous discussion implies that a select group of students profoundly influenced Chester Werkman's scientific career. This effect is reflected in the rate of research publications emerging from the Werkman laboratory.

One way to visualize publication rate is to calculate the cumulative percent of publications, determined by expressing the number of publications in any one year as a percentage of an individual's total lifetime publications. These yearly percentages are summed over time, and the sums are plotted versus the year. This approach was used to analyze the publication rates for both Werkman and Wood – as well as that of Merton Utter, another of Werkman's more productive students – and the results are summarized in Figure 1.[93]

The data in Figure 1 demonstrate that Werkman's rate of publication initially began to increase prior to Wood's joining the laboratory in 1931 – an increase that may reflect the work of O. L. Osburn, another of Werkman's highly productive coworkers. As the contributions of a small group of around seven or eight colleagues became significant, the publication rate continued this marked increase. However, as this group of workers left the laboratory, Werkman's ability to sustain the high rate of publication markedly decreased and approached that of his early years at Iowa State. In comparison, the publication rates for Wood and Utter were relatively constant throughout their careers; indeed, in both cases, the rates of publication actually *increased* during the later parts of their careers. It is also important to recognize, however, that the decrease in Werkman's publication rate can only partially be attributed

[92] Eric Fowler, letter to the author, October 1, 1994.

[93] While it would be desirable to carry out such an analysis for all of Werkman's students, this is a difficult task. One difficulty rests in the absence of complete bibliographies for all of these individuals. A greater difficulty, however, is that Werkman's students often pursued other, quite varied, careers where publication was not as important. For example, Howard Reynolds (who was in the Werkman laboratory during the same time as Wood) spent much of his professional career working for the USDA and had around seventy-five publications (many of which were internal USDA reports) when he died (pers. comm. from Sandra [Reynolds] Miller); thus, his copublication with Werkman accounts for almost 20 percent of Reynolds' total publications.

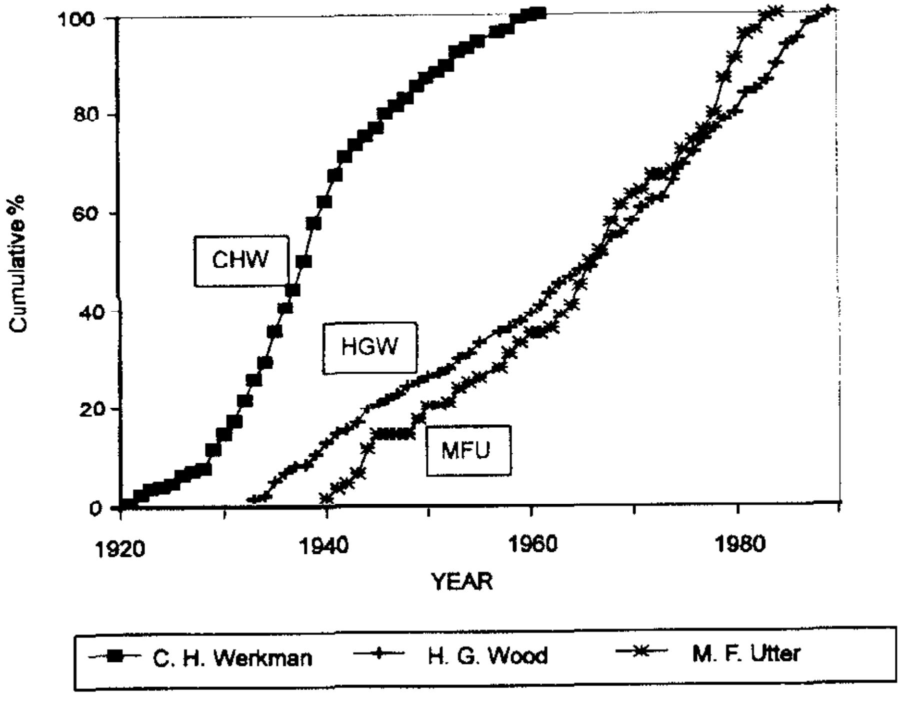

Figure 1. Cumulative publication rates for Werkman, Wood, and Utter. (Data from R. W. Brown, "Chester Hamlin Werkman, 1893–1962," *Biog. Mem. Nat. Acad. Sci.*, *44* [1974], 328–370; H. G. Wood, *Curriculum Vitae – 1991*; and H. G. Wood and R. W. Hanson, "Merton Franklin Utter, 1917–1980," *Biog. Mem. Nat. Acad. Sci.*, *56* [1987], 474–499.)

to the departure of a select group of students from his laboratory: administrative duties as department chair, and an increasing series of health problems, also contributed to his inability to sustain such a high rate of research activity.

Publication data provide other ways to explore individual scientists' interactions with their collaborators, for we can ask questions about those with whom they coauthor their publications.[94] The data in Table 3 summarize the most frequent coauthors on publications by Werkman, Wood, and Utter. Because each investigator had numerous collaborators, the data are shown only for those colleagues whose combined contributions represent approximately 50 percent of each individual's total publication effort.

[94] Calculating the frequency of co-authorship is complicated by the fact that the number of co-authors on an individual paper varies greatly both over time and by practice of individual primary authors. To correct for these variables, the frequency of co-authorship reported in Table 3 was determined as follows. The number of papers involving each co-author was divided by the primary author's total number of publications. This number was then multiplied by the ratio of (total papers)/(total authors) for each primary author and expressed as a percent.

Table 3. Frequency of coauthorship with colleagues of Werkman, Wood, and Utter.

Principal author					
Werkman (50% of total)		Wood (50% of total)		Utter (50% of total)	
Wood, H. G.	12.4%	Wood, solo	8.4%	Utter, solo	7.5%
Werkman, solo	6.3%	Werkman, C. H.	8.1%	Scrutton, M. C.	7.5%
Osburn, O. L.	4.8%	Stjernholm, R.	3.4%	Werkman, C. H.	5.9%
Reynolds, H.	4.2%	Ljungdahl, L. G.	3.0%	Wood, H. G.	3.8%
Utter, M. F.	3.9%	Jacobson, B.	2.4%	Taylor, B. L.	3.8%
Brown, R. W.	2.7%	Goss, N. H.	2.1%	Kurahashi, K.	3.2%
Hemingway, A.	2.7%	Kumar, K. G.	2.1%	Keech, D. B.	3.2%
Michelson, M.	2.7%	Hemingway, A.	1.9%	Weinberg, M.	2.7%
Nier, A. O.	2.7%	Nier, A. O.	1.9%	Bernofsky, C.	2.2%
Silverman, M.	2.7%	Ahmad, F.	1.5%	Cohen, N. D.	2.2%
Stone, R. W.	2.7%	Kellermeyer, R. W.	1.5%	Barden, R. E.	2.2%
Brewer, C. R.	2.4%	Lorber, V.	1.5%	Frey, W. H., II	1.6%
		Pezacka, E.	1.5%	Young, M. R.	1.6%
		Ragsdale, S. W.	1.5%	Isohashi, F.	1.6%
		Allen, S. H. G.	1.3%	Freytag, S. D.	1.6%
		Katz, J.	1.3%		
		Utter, M. F.	1.3%		
		Davis, J. J.	1.1%		
		Lifson, N.	1.1%		
		Schambye, P.	1.1%		
		Schulman, M.	1.1%		
		Willard, J. M.	1.1%		
		Clark, J. E.	0.9%		

Sources: For Werkman (230 papers): R. W. Brown, “Chester Hamlin Werkman, 1893–1962,” *Biog. Mem. Nat. Acad. Sci., 44* (1974), 328–370. For Wood (284 papers): H. G. Wood, *Curriculum Vitae – 1991*. For Utter (186 papers): H. G. Wood and R. W. Hanson, “Merton Franklin Utter, 1917–1980,” *Biog. Mem. Nat. Acad. Sci., 56* (1987), 474–499.

This analysis provides insights into ways that individual collaborators can dominate the research output of a particular investigator, and several points are immediately obvious. First, Wood and Werkman, together, coauthored twice as many papers as Werkman authored alone. This observation further reflects the profound effect that the associate, Wood, had on his mentor’s career. Second, the papers that both Wood and Utter coauthored with Werkman account for a significant portion of their individual total publication records, suggesting that the time they spent in Werkman’s laboratory ultimately played an important role in their scientific careers. Finally, after leaving Werkman’s laboratory, both Wood and Utter tended to coauthor with a larger number of colleagues than did Werkman: while eleven individuals helped coauthor 50 percent of Werkman's total publications, twenty-two coauthors were involved in Wood's publication record, and fourteen in Utter's.

Part of the professional impact of student-professor collaborations may arise from the fact, as observed by Jane Maienschein, that in such collaborations, "responsibility and credit for publications resulting from the work are not always clear, and a variety of patterns have appeared."[95] Apparently concurring with Fruton's view of the idiosyncratic nature of mentoring,[96] Maienschein suggests a continuum in the patterns of student-professor relationships: at one extreme are professors who rarely copublish with their students; at the other extreme are students who remain within "their major professor's shadow and never achieve the level of primary collaborator even when they deserve such a designation."[97]

However, the relationship between Werkman and his students – especially Wood – seems to fall outside this continuum. Although Wood began in the role of traditional graduate student, the structure of Werkman's laboratory was such that he soon became a dominant intellectual force and the research group's leader. Nevertheless, despite achieving this status, he had no independently published work and was never allowed to formally direct graduate student research – both activities recognized as signs of an independent research investigator. And yet despite this apparent anomaly of Werkman's control, the broader scientific community seemed to recognize clearly that Wood was a major creative force in the laboratory (as witnessed, for example, by his winning of the Eli Lilly Award).

Conclusion

Many individuals in science are often ambivalent about what it is that we do. On the one hand, we like to talk about the scientific method as a strictly objective practice firmly grounded in the empirical world. We ask questions about nature, we formulate hypotheses to answer these, and we design tests for the hypotheses. If the test supports the hypothesis, we believe that we have discovered some *truth* about nature. The process has the appearance of a truth discovery machine, devoid of human passion and interests. In a greatly abridged form, this is what Philip Kitcher refers to as the "legend of science."[98] Yet, anyone who has spent more than a day in serious scientific investigation knows that science involves personality forces that transcend

[95] Maienschein, "Why Collaborate?" (above, n. 6), p. 174.
[96] Fruton, *Scientific Style* (above, n. 9), p. 2.
[97] Maienschein, "Why Collaborate?" p. 176.
[98] Kitcher, *Advancement of Science* (above, n. 5), p. 3.

such objectivity and empiricism. Each person who practices science does so in a style that is in part unique and evolves out of our relationships with our mentors and other colleagues. More often than not, an individual investigator's personality and worldview significantly affect the science he or she produces. This does not mean that the work produced is better or worse; it simply means that the style of practice that produced the work is different for each individual.

This inference also does not mean that the practice of science is inherently flawed and unable to formulate objective views of the world. Regardless of the social context from which they emerge, all scientific assertions must ultimately correspond to some aspect of objective reality. This conclusion is grounded in the social environment within which science is practiced. For example, David Hull has cogently argued that a scientific idea's value rests in its usefulness to other members of the community; ideas that fail to conform to a developing communal view of objective reality are useless to other members of the community, and are soon discarded.[99] In Hull's picture of science, it is this utilitarian value of ideas for other workers in the community that allows the entire enterprise to develop an increasingly coherent body of objective knowledge.

Few scientific careers illustrate the idiosyncratic nature of scientific style better than those of Chester Werkman and Harland Wood. If Werkman was the detached professor, isolated from the laboratory, who allowed his research associates to find their own means of survival, Wood pursued a different approach. In 1985 he stated (with a not entirely veiled allusion to Werkman): "Many highly successful scientists desert the laboratory bench early in their careers . . . my own goal has been to remain personally active in the laboratory as long as I am involved in science."[100] As a research mentor, Wood developed an ability to allow his associates enough freedom so that they were able to mature to their fullest – but because he was actively working on some aspect of the problem in the laboratory himself, he was able to provide direct and immediate guidance when needed.

These divergent styles are, for me, illustrated by various photographic images. As reflected in a photograph made a few years after his appointment as chairman of Bacteriology at Iowa State, Werkman was perhaps far closer to a more modern style of science practice. Although the photograph was clearly posed, it shows Werkman sitting behind an immense desk working on some papers. With the exception of two pens in holders, a book, and a telephone, the desk is aseptically clean. He appears as the consummate grant manager who was able to get the money, find excellent people, and turn them

[99] Hull, *Science as a Process* (above, n. 2), p. 4.
[100] Wood, "Then and Now" (above, n. 26), p. 2.

loose to do the best work they were capable of doing with little intervention or direction on his part.

Although Wood served a wide variety of administrative roles, both within the academic system as well as in the broader scientific community, he remained committed to the laboratory for all of his life; his heart and passion were in laboratory work. Two photographs capture that passion for me. One was made in Werkman's laboratory, shortly after it had been set up for work with heavy isotopes of carbon, and shows Wood, wearing a black rubber chemist's apron typical of the time, intently sitting at the mass spectrometer that he had helped to construct. The second picture, made several years later, is of Wood milking a cow in a research barn at the University of Illinois: the experiment was part of a collaborative study of lactose metabolism in the cow's udder, and because he grew up on a farm, Wood was one of the few members of the research group who knew how to milk the cow that was central to the experiment. Both images capture the intensely personal dedication, commitment, and joy that Wood brought to scientific research. At the time of his death, his research program was one of the most highly funded in the department, even though he was eight-five years old and in an emeritus status. The high funding was of little significance to him, except for the fact that it allowed him to do what he loved: to sit at the laboratory bench rather than at a desk.

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