RATS, FATS, AND HISTORY

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In 1883 a Department of Agricultural Chemistry was founded at the University of Wisconsin in the city of Madison. One hundred years later seems a fitting time to look back, to gain some perspective on the fortunes of that academic undertaking. It is in looking back that I discern an intriguing wave in the tide of time. Although in the first 30 years there was much of interest, I shall leave that span to others. In 1913 the department gained a new sense of presence, as bricks and mortar were laid to form what is now known as the "old building." The department's title, "Agricultural Chemistry," was inscribed in the stone lintel over the entrance door, and is found there still, even though, since 1938, the department's title has been "Biochemistry." I mention these facts with no hope of startling anyone, for they are well known, but rather to establish the time frame for that special segment of the history of the department, that wave that I think I have discerned and that I wish to address.

It is my thesis that 1913, the year the lintel was set, was a watershed year for agricultural chemistry, for the newly emerging sciences of human and animal nutrition, and for the ambitions of a remarkable group of chemists in the department at that time. The key discovery that marks this watershed year was the recognition of what came to be known as the fat-soluble vitamins. The first of these was vitamin A.

What I now propose is to delineate, as best I can, the historical and philosophical roots of this discovery, and try to understand thereby why the fat-soluble vitamins were first discovered in Madison; why it was in 1913; and how the people who did it came to do it just then.

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Why Madison?

In thinking about the questions raised by recognition of a certain event—say, the discovery of vitamin A—is to link that unique event with specifications of time (1913) and place (Madison, Wis.). There is a school of thought that says that such a discovery was bound to take place, sooner or later. Further, says this school, it is the total activity of the scientific community, committed to certain principles of outlook and procedure, that insures the slow but certain unfolding of the laws of nature. Progress, at times, may be slow, but it is certain. By these lights, then, if vitamin A was discovered in Madison, then Madison was just the locus of the last, but sufficient, effort. Science, says this view, progresses by increments, and there is nothing special about Madison in the matter of the vitamin A discovery. Madison was the scene of the final increment.

As scientists, then, by this view we are actors in scenes of frenetic activity (which may be an accurate description at times) and are like the oft-remarked monkeys that in large numbers, and over long periods of time, by jumping up and down on the keys of typewriters, could produce all the books in the British Museum. If, at times, the product of our own labors seems ridiculously small, then perhaps we are involved with a bad set of typewriters.

This view of the history of science, which is widely held by the general public (if it thinks about it at all), is a comfort to many since it is so "democratic." Scientists, to change the simile, like ants, seem to be very busy in their mysterious comings and goings, but just what is on their minds is not at all clear.

Let me restore our spirits. We are not monkeys, and we are not ants. The discovery of vitamin A, at Madison, was not an incremental event in the history of science. It was a supremely human achievement, it was unique, and it took place at Madison for very special reasons. It was a revolution.

At this point you find me still warily circling my subject, the discovery at Madison of vitamin A. But now I have introduced a word, "revolution," that reveals the plan of what follows, and reveals my debt to a historian and philosopher of science, Thomas S. Kuhn [1].

In 1962 Thomas Kuhn published his remarkable book, *The Structure of Scientific Revolutions*. It is his view of the nature, causes, and consequences of revolutions in basic science concepts that, it seems to me, is the most satisfying framework for our understanding of what, precisely, we are engaged with here: namely, the mode and meaning of the discovery of the fat-soluble vitamins, beginning at Madison in 1913. In the years since I left Madison in 1939 I have read, from time to time, books aspiring to explain the nature of scientific discovery. I naively thought that I might find therein fruitful guides for my own exertions at the laboratory bench. But all, it seemed to me, left me standing outside the process, admonished by my betters to be struck with awe, but no better armed to understand scientific progress than before. For me, Thomas Kuhn changed all that, and since his insights are the road we will now travel, it will be expeditious to briefly sketch his scheme of things.

Most of our lives as scientists, according to Kuhn, we are busy with what he calls "normal science." This means getting on with solving the problems that are reared within a conceptual framework that is silently accepted by the field of science in which we are working. Within this framework, professors and their students are all busy poking into every nook and cranny of this framework, seizing on "problems" cast up by the framework, defined in terms of the framework, and attacked by methods prescribed by the framework. "Answers" are found, and several generations of professors and doctoral candidates are busy indeed.

But, inevitably, a crisis arises, according to Kuhn. The prescribed and accepted conceptual framework does not accommodate and provides no means of resolving new and troubling experiences in the observations rightfully embraced by the field which is being so assiduously tilled. It is to the solution of this kind of crisis that we really should reserve the term "discovery." For, by the very definition of the situation I have just described, that former concepts would not work, resolution of the crisis inexorably must come from the new and novel. A new conceptual framework is constructed, the new framework is seen to be productive, it is adopted, and professors and students are busy once again with the many new tasks, and all are again involved in "normal" science.

This, in very brief, is the Kuhnian scheme of things. In addition to the special definition we have given to "normal" science here, there is one more term that needs introduction for our purpose. It was an old word, but Kuhn has given it a new life and utility. This is the word "paradigm." A paradigm is a model or pattern and, as used by Kuhn, concisely conveys the sense of the framework that, in its acceptance, provides a silent compendium of how to proceed with the tasks of "normal" science. "Normal" scientists do "normal" science by following the accepted paradigm for their field. When the paradigm becomes exhausted, a crisis is at hand. The paradigm no longer works as a productive guide. Only the introduction of a new paradigm, a true discovery arrived at by an acceptance, however reluctant, of the unknown, fotfowed by exploration of alternative and fresh frameworks, resolves the crisis and makes possible the resumption of "normal" science.

Let me now cast my story of the discovery of the fat-soluble vitamins in Kuhnian terms. By 1913 the field of nutrition was in crisis. Chemical analysis of foods (the accepted paradigm) had uncertain, and at times completely erroneous, predictive powers for the assembling of rations for farm animals—with obvious economic consequences. The crisis was resolved in terms of a new paradigm: the testing of the nutrient value of foodstuffs by feeding to an experimental animal, the rat. The new information thus gained resolved the crisis, acceptance of the new conceptual framework quickly followed, and "normal" nutritional science resumed.

Let us now return to the real world of Madison in 1913.

The crisis in nutrition, as described above, was the failure of chemical analysis of foodstuffs to provide information capable of predicting the ability of assembled rations to nourish farm animals. This failure had important and obvious economic consequences. Agricultural experiment stations smarted under this failure, and the frustration at the station at Madison was as intense as any.

If the sense of crisis was slow in coming it was certainly very real by the late nineteenth century, and there now arrived in Madison, in 1888, just 5 years after the founding of the department, the necessary iconoclast who would clear the way. This was the chemist, Stephen Moulton Babcock, who came to Madison from the New York State Agricultural Ex periment Station at Geneva. It was there that he had become thoroughly aware of the serious inadequacy of chemical analysis to provide the information that a science of nutrition demanded. Paul de Kruif has told this story well [2], so there is no need to dwell on it. But two events now occurred in the life of Dr. Babcock which, by hindsight, we can now see as forming the preconditions which led to the discovery of vitamin A. The first of these was, of course, the designing of the Babcock test for butterfat in milk. This put the dairy industry of Wisconsin, of the United States, of the world on a sound economic base, and as a governor of Wisconsin, W. D. Hoard, remarked, "The Babcock Test has made more dairymen honest than the Bible has ever made." The watering of milk became a stupid thing to do when one was paid for the butterfat and not for the weight of the milk. The Babcock test made Babcock world-famous, but, for our purpose here, this is not the important point. The important point is that Babcock was not only famous, he was now a heavyweight in the political considerations which always bore in on state-supported institutions. When troubles brewed in the legislature, with ominous consequences for the university, smart deans and presidents asked Babcock to come with them to explain matters to the farmer-legislators of the dairy state. There Babcock was greeted with awe and listened to with respect.

Babcock's role in the story of vitamin A was thus twofold: he brought the required spirit of iconoclasm to the study of nutrition, and, by virtue of his fame as the designer of the Babcock Test for Butterfat, he wielded considerable political power. And this power was capable of being used within the university as well as without. Its use within the university is the next step in our story.

Babcock had brought with him from the experiment station at Geneva an interesting idea. It was, in a sense, a retreat; but it was a retreat to the high ground. If chemical analysis was failing to provide information capable of accurately predicting the nutritional value of foodstuffs, then before hazarding all on chemical analysis one ought to look at the feeds themselves. For many good economic and empirical reasons, farm animals were fed mixtures of foodstuffs, and the struggle always was to devise the most nourishing and simultaneously the most economic combination. Chemical analysis of the separate foodstuffs had provided a kind of common denominator for these purposes. From the chemist's view a given level of, say, protein was achieved by calculation from the analytical results obtained from the various items. A Kjeldahl nitrogen analysis was a Kjeldahl nitrogen analysis, and if you wanted to know the protein this denoted, you multiplied by 6.25. It did not matter to the chemist whether you were talking about wheat, corn, oats, or what. "But, ah," said Babcock, "what if it did matter?" This made agricultural chemists of the day very angry, and they appointed committees.

Babcock's answer was to design an experiment. "Try one foodstuff at a time, feed it to a cow for a long time, and see what happens." Well, people were not handing out cows, and so Babcock's idea had to wait until he got to Wisconsin. Twenty years after he had his idea, Babcock got his cow—in fact, two of them. He got them from the professor of animal husbandry at Madison, W. L. Carlyle. Babcock fed one a ration of oats, oat straw, salt, and water. The other cow got a similar mixture, but only corn. In 3 months the cow on oats died, and the other, on corn, looked pretty peaked. Carlyle took his remaining cow back and returned her to health on the station official ration. Babcock did not publish.

Six years later, in 1907, Babcock got his second chance, this time not with two cows but with 16. The results, the famous Research Bulletin no. 17 of the Wisconsin Agricultural Experiment Station, appeared 4 years later, in 1911 [3]. Sixteen calves were divided into four groups of four: three groups were fed single-grain rations, balanced to identical chemical analysis by various amounts of grain, gluten, stover, straw, etc., but all from the same plant: oats, corn, or wheat. The fourth group received a mixture of all three. The results showed that identical chemical analyses failed to predict the nutritional results. The plants were different, unambiguously different, as sources of nourishment; and these differences were not explicable in terms of chemical analysis, for this had been carefully adjusted to equality, each group with the others. This was Babcock's iconoclastic contribution; this was the experiment that shattered the icon of the chemist as the arbiter of matters nutritional; and, in Kuhnian terms, a paradigm collapsed.

Paradigms do not collapse overnight, and scientists do not rush into the streets crying "My God, what shall we do?" Things take a little longer. The Babcock single-grain experiment was begun in 1907, and the results were published in 1911. It is interesting that the 1911 publication did not have Stephen Moulton Babcock among its authors, although there can be no doubt that the idea was his. The 1911 authors were E. B. Hart, an agricultural chemist newly come to Wisconsin in 1906 from (where else?) the experiment station at Geneva, New York; E. V. McCollum, an organic chemist from Yale, who had had no success in finding a job since obtaining his doctorate in 1906 and was now hired by Hart as an instructor in agricultural chemistry; Harry Steenbock, in 1907 a student in agricultural chemistry enrolled in McCollum's first course at Madison (McCollum awarded him an A); and G. G. Humphrey, professor of animal husbandry. Each of these men has an interesting history, but in pursuing the trail to the discovery of the fat-soluble vitamins we are led to focus our attention on McCollum. He has given us an autobiographical account [4] of his career and, drawing on it, I think we can identify him as the self-aware designer of the new paradigm for nutritional research. And it is to that paradigm we now turn our attention.

Hart, successor to Babcock (who had stepped down from administrative duties), hired the young McCollum to perform the innumerable analyses incessantly demanded for the formulation of the rations descending into the stomachs of the 16 cows. It was an analytical treadmill, and McCollum soon tired of it.

McCollum started work at Madison as Hart's subordinate on July 1, 1907. When he saw the cows on the single-plant experiment he was impressed and awed by his responsibility and opportunity. For there were amazing contrasts to be explained. The wheat-fed cows were stunted and blind. All of their calves had been born dead. The oat-fed cows were somewhat better off, but although their calves were carried to term and were born alive, they soon died. Only one was a survivor. But the corn-fed cows did well, even better than the mixed-ration controls. All of the cows had been fed rations of the same chemical composition, but the results were dramatically different. What was the basis of the difference? In time McCollum found an answer to that question, but before he could do that he had to invent some new ideas and some new methods of grappling with nutritional problems. First there came a time of seasoning.

It was chemistry of a different kind which provided the seasoning of McCollum. It was the chemistry of the relationship between the young McCollum and the emeritus Babcock. Embedded in the humorous approach to life and living of the older man were the factual nuggets of a very real world. Babcock was lighthearted, but he was, at the same time, capable of communicating some serious ideas with an unforgettable impact. Here, for example, is a brief excerpt from McCollum's autobiography that shows the influence of the older on the younger man [4, p. 116]:

> In time I shared appreciation of the humor of the advice Dr. Babcock gave Dr. Atwater, then the outstanding authority on human nutrition. He recommended that instead of feeding pigs on farm crops it would be cheaper to feed them soft coal. When such coal was analyzed by the current food-analysis procedures the results indicated that it was a well-balanced food. It contained nitrogen. Most proteins are 16 percent nitrogen. Multiplying nitrogen content by 6.25 gives protein content. Soft coal contains ether-soluble substances which in the food analysis, without further identification, was called fat. Other fractions determined in the ordinary practice could be considered sources of energy. Hence by the criteria of fne chemical rnethods of food analysis bituminous coal had high food value. Dr. Atwater did not like the analogy and was irritated by Babcock's treating a serious subject with levity.

Babcock's humor made his iconoclastic views palatable and, it seems safe to surmise, encouraged the young McCollum to the independence of thought so necessary for the invention of new ideas. But McCollum brought something of himself to the task, too. This was his indefatigable scholarship.

Of all the scientists who have spent their allotted time in the department, I think it is fair to say that McCollum was the deepest read and had the greatest sense of history. There is a legend that at the end of each working day he took home a few volumes of the bound journals of publications which seemed to him might improve his understanding of the problems he faced in his work. The legend further says that he began with volume 1 and worked his way to the last, and then current, volume for each journal. As a graduate student here I went to the Agricultural Library to check on this. The legend was confirmed. I found many of the older journals, in their earlier volumes, had only one entry on the card in the jacket inside the cover. That entry was "E. V. McCollum."

Now, as I understand it, McCollum did not read every paper in every journal. Rather, he browsed through the pages and when he saw a title indicating something of interest he stopped and read it, and then continued on. By means of such prospecting McCollum finally struck gold. The "gold" was the 37 volumes of a Cerman publication, Maly's *Jahresbericht über die Fortschritte der Tier-Chemie.* McCollum had seen the file of this yearbook when he was at Yale, was delighted to find all of the series at the Agricultural Library at Madison, and wound up buying the whole set to keep for study at leisure at home. And it was in these volumes that he found information that was not in textbooks or in the current journals. As McCollum remarks in his autobiography [4, p. 117], "From Maly's *J'ahresbericht* I learned the history of constructive thought and experiment in animal and plant biochemistry between 1870 and 1907."

It strikes me as significant that McCollum here links "history" and "constructive thought" with "experiment." History and philosophy ("constructive thought") were joined in McCollum with the experiments of the scientist.

And just what did this browsing in volumes running back 37 years accomplish? Clearly, it led the way to the new paradigm for nutritional research that was to yield such rich returns. But let McCollum tell of his prospecting amid the gold of Maly's yearbook [4, p. 117]:

> Leafing the pages of these volumes I came upon the abstracts published by thirteen authors between 1873 and 1906. In them were described efforts to nourish small animals, mostly mice on diets composed of isolated and purified proteins, carbohydrates, fats, and inorganic salts. I was struck by the fact that in every instance in which small animals had been restricted to such "purified" diets they promptly failed in health, rapidly deteriorated physically, and lived only a few weeks. I made notes and reflected on all these experiments. I concluded that the most important problem in nutrition was to discover what was lacking in such diets. They contained everything that chemists, physiologists, and medical men considered essential, yet when fed to mice they proved wholly inadequate for the maintenance of life and health.

McCollum now had his great idea. He could get out from under the drudgery of those endless analyses connected with the consuming cows, and better yet, he could realistically tackle the problem of preparing adequate supplies of purified foodstuffs which would sharpen the experiments immeasurably. Small animals such as mice ate by the gram and not by the kilo, as did the cows. A whole new world of experimentation beckoned. Late in 1907 McCollum broached his idea to Hart, suggesting that for experiments with purified foodstuffs they use rats, instead of mice, because of their omnivorous feeding habits and more convenient size. Mice were, perhaps, a little too small.

Hart, in a word, did not take kindly to the idea that after only a few months the new instructor was proposing work that would take his time away from the task he had been hired for, to investigate why the rations from single-plant sources differed so greatly in value. One can imagine the cold water that poured forth from the department head.

A disappointed McCollum now found his champion, the redoubtable Babcock. For Hart, and the dean of the College of Agriculture, H. L. Russell—all gave way to the endorsement of Babcock, and McCollum was on his way, tolerated if not wholeheartedly approved by his superiors. But when McCollum placed a requisition for $2.00 worth of wire-mesh screen to make some cages for the rats, Hart refused to sign. McCollum paid for the mesh out of his own pocket. His salary at the time was $1,200 a year.

Wild gray rats, trapped in the old horse barn on the station farm, proved too wild, too vicious for experimental work, so McCollum bought a dozen young albino rats from a pet dealer in Chicago and started the first rat colony ever to be used for experimental purposes. I think Hart became convinced of the doggedness of his new instructor, for as the colony began to outgrow the makeshift cages, he approved an allocation of $50 for more and better cages to be made in the university carpenter shop.

The switch to experiments with rats as a way to investigation of problems of nutrition now seems so simple, so mundane. But let me emphasize that it was the first step, an important step, in the forming of the new paradigm.

The next step was not so easily clarified or reached. McCollum had seen the merit, indeed the'strStegie necessity, of designing experimental diets from purified foodstuffs. Slowly it had to be learned that chemical purification, the elimination of confounding materials in the natural sources of these materials, was the crux. As purification of such items as protein sources proceeded, or as different natural sources of fats were compared, it became evident that purification, and even, in the case of fats, the choice of starting materials had profound effects on the capacity to nourish. The hay pile was now squarely in front of McCollum, but where were the needles?

As we all now know, many needles were found in due course, and we shall address the discovery of the first fat-soluble vitamin, vitamin A, momentarily; but it should not be lost on us that the seminal event was not the discovery of vitamin A, important though it was—rather, it was the working toward, and finally the clear statement of, the new paradigm for nutritional research. Like so many scientific advances, the true import became clearer with the advantage of a bit of hindsight. It is not surprising, therefore, that the clear statement of what McCollum called "the biological method of analysis" was published in 1915, 2 years after the watershed year of 1913, and was restated more formally in 1925 [5]. We can summarize it here as follows: A nutritionally inadequate diet, of natural materials or assembled from chemically described, purified materials, is supplemented, singly or multiply, by additions from other natural foodstuffs. The supplements identified as improving nutritional performance, usually by the criterion of improved growth, are chemically fractionated, and one is led ultimately thereby to the identification of the chemical nature of the successful supplement. And for a quarter of a century that paradigm led to a series of discoveries and the era of modern nutrition.

There are several elements of the new paradigm which, I think, bear emphasis. The evidence of nourishing properties of dietary elements was sought in the favorable response of physiological parameters, such as increased growth of the weanling rat. Chemistry was used, not to provide analytical data of the foodstuffs for interpretation by standards accepted a priori, but for the purification and fractionation of the foodstuffs used in the diets themselves. And with the relatively small amounts needed for small animals, these requirements could be met in the laboratory.

There is another aspect embedded in the new paradigm that, I think, has simple but weighty philosophical consequences. By beginning, as one must, with diets of natural foodstuffs, the superiority of, say, diet I to diet II by previous paradigms was sought by quantitative comparisons afforded by the results of chemical analysis for known constituents. The great power of the new paradigm was that it made no assumptions a priori as to the nature of substances responsible for the observed differences between diet I and diet II. They could, in the end, be substances already known, or, more exciting, they could be items completely unknown in their nutritional significance hitherto. What is more, the new paradigm was completely unambiguous as to where the new substance, if such it was, lay hidden. The unambiguous operation of adding, of supplementing, made it certain that if favorable response occurred, then the important substance or substances were to be sought in the supplement. If the supplement was the haystack, then it was up to the chemist now, by his fractionation methods, to find the needle.

Right here, allow me to comment on the role of biochemistry in these events. Just when a science of nutrition was in need of increasing sophistication and increasing powers of resolution in the methods of chemical fractionation that were now clearly needed, biochemistry, for its own ends, began just such developments for the isolation of small amounts of labile materials from natural sources. I believe that simple fact is the reason why a new science of nutrition was born and nurtured in a department of biochemistry, even if that name came later. Indeed, it was the startling nutritional discoveries made in biochemistry departments that drew favorable attention to them and even some support. It was a matter for some preening. It has, of course, for the moment ended. Why this should be so is a matter I will comment on below. But now we must return to 1913, the first year that the new paradigm produced the memorable event known as the discovery of vitamin A.

Why 1913?

In June 1913, McCollum and Marguerite Davis sent to *the Journal of Biological Chemistry* the manuscript of their milestone paper, "The Necessity of Certain Lipins in the Diet during Growth." In this publication [6] it was clearly shown that all fats were not nutritionally equal when it came to nourishing young rats on a diet assembled from purified materials. Protein, carbohydrates, and mineral salts furnished a base to which fats of various kinds were added. Butterfat and the ether extract of egg yolk supported growth, but fats such as lard or olive oil did not. This was surprising since up until then fats were regarded merely as concentrated energy sources in the diet. And on this basis all digestible fats should be equal. But McCollum and Davis had shown that they were not.

The question of the nature of this difference was next resolved unambiguously when McCollum and Davis [7] showed that the growth-promoting lipid was in the relatively small residue of the fat that was not saponifiable, "the non-saponifiable fraction," and that this fraction could be transferred to olive oil, changing it thereby from a fat that failed to support growth into one that did. This was incontrovertible evidence that an ether-soluble growth-promoting substance, a "lipin" in the terminology of the day, was capable of being separated from its source in a natural fat, and of being transferred to another, nongrowth-supporting fat and, by this act of transferring, bringing with it the growth-promoting property. History had been made, and as McCollum later exulted in his autobiography [4, p. 134], "We had discovered vitamin A."

The dam had been breached in Madison, in 1913, and the river of further successful investigation in Madison, to this very day, swelled into a torrent from laboratories around the world. We will not detail here that flood of publications. Suffice it to say that McCollum went on, in July 1917, to the new School of Hygiene and Public Health as its first professor of chemistry. But in Madison a new age was dawning in nutrition research. Hart and Steenbock were the leading and cutting edge of progress in the years that followed. Steenbock and his co-workers furthered the vitamin A story with an elucidation of the role of the carotenes as the provitamin A of the plant world that animals converted to vitamin A by their own metabolism. And, of course, it is well known how Harry Steenbock traced the action of ultraviolet radiation in activating vitamin D precursors into antirachitic activity. The vitamin D story goes on at Madison even today, but it is not too early to discern the historical significance of the work by DeLuca and his co-workers that has forged a clear link between a metabolically derived product of vitamin D (the dihydroxy derivative) and the domains of endocrinology, in which the vitamin D derivative functions as a hormone. As for vitamin A, there has been an explosion of interest and activity surrounding the notion that vitamin A (retinol) or provitamin A (beta-carotene) can function as an antineoplastic agent [8, 9].

The discovery of the first fat-soluble vitamin had been announced, as described above, in the landmark paper of 1913 by McCollum and Davis. I want now to digress, to shed what light I can on the history of Marguerite Davis, who was McCollum's assistant and collaborator for 7 years, from 1910 to her unexplained resignation in 1916, just before McCollum went to his new post at The Johns Hopkins. During this period Davis was the junior coauthor with McCollum in the publication of 10 research articles, nine of which appeared in *the Journal of Biological Chemistry*. (For these facts, as well as others in the life of Davis, I am indebted to Harry G. Day, professor emeritus of chemistry, University of Indiana [10].)

Davis remains a somewhat mysterious figure, and there are many gaps in the historical record. But she is certainly entitled to a place in any history of this Wisconsin story. Davis was a Wisconsin native, born in Racine on September 16, 1888. She died in that city, just 2 days after her seventy-ninth birthday, on September 18, 1967. Originally enrolled at the University of Wisconsin, Davis transferred to the University of California at Berkeley in August of 1908 and received a B.S. degree in natural science on May 17, 1910. Her mother died, probably before Marguerite's graduation, and she returned to the Midwest to make a home for her father, a retired physician of Racine now living in Madison, where he pursued botanical studies. This task was not completely fulfilling for Davis, and on the advice of the formidable Abby L. Marlatt, head of the Department of Home Economics at Madison, she presented herself as a kind of free-lance graduate volunteer to McCollum, who set her to learning the biochemistry of the day. But soon she learned of the new and struggling rat colony of McCollum's and offered to take on the care of it. McCollum was delighted to be relieved of the chore and, with her help, expanded and sped his program of experiments. McCollum repeatedly and frequently acknowledged his debt to Davis.

Apparently the Department of Agricultural Chemistry felt no such debt, for although McCollum requested a salary for Davis each year, each year Hart denied the request. The request was denied, Hart felt, because Davis was not sufficiently trained to be placed on staff. In the sixth year Hart relented (her training was now adequate?), and Davis received $600 for her year's work. Davis resigned shortly thereafter. I do not know whether the two events were connected.

It may be that this selfless dedication to her father and to McCollum's ambitious program was all of a piece with a diffident acceptance of life's burdensome struggle for an intelligent woman of her day. It is very probable that this was accentuated by the trauma, at the age of 10, of being severely burned when her clothing caught fire while she played at a bonfire. Although the record is not clear, these burns left her with a physical handicap, but apparently, from those few accounts we have, she suffered no facial disfigurement.

After stints at the University of Chicago and the Home Economics Laboratory at Madison, where she published five articles in the period 1920–1923, Davis became an authority on vitamin A assay and was invited to set up such studies at the laboratories of E. R. Squibb and Sons in New Jersey. In 1926 Davis was at the New Jersey College of Pharmacy at Rutgers University. Thereafter the trail of Davis's life becomes shrouded, but apparently she returned to Racine and lived a life of retirement. She was not an enthusiastic correspondent and failed to answer many letters addressed to her. Racine was not unaware of her career in the founding of a science of nutrition and took pride in her restoration, completed in 1955, of the family residence which had been built in the 1840s. The home overlooked Lake Michigan and here Davis lived out her days.

The history of McCollum, his dedicated assistant, Davis, and the fateful year of 1913 at the Department of Agricultural Chemistry, all bear witness to the revolution in nutritional research that was born there. Again, using the grammar of the history of science as formulated by Thomas Kuhn, we can say that the crisis, of contradictions embedded in the old paradigm of chemical analysis of foodstuffs as a predictor of nutritional merit, was resolved and replaced by the new paradigm of the use of a small animal, the rat, and the principles of the biological method of analysis.

The floodgates were now opened to a river of new knowledge of nutrition. We have given a small amount of time here to describing the first discovery, of vitamin A, the first fat-soluble vitamin. Indeed, the whole notion of vitamins now had an operational base solid enough for the tracking down of a whole array, a process that would, as "normal science," occupy a host of professors and their laboring assistants for the next 4 decades.

Another consequence of the new paradigm was that it led investigators into a world of much smaller dimensions than had been dreamed. The now-discredited reliance on chemical analysis had always taken satisfaction in the almost mathematical completeness of the quantitation. When all of the items, the protein, carbohydrates, fats, and minerals were totted up, the total came reassuringly close to the 100 percent mark. But the new paradigm showed that the mysterious substances being brought to light lay in that tiny sliver of the unapprehended. This new world of importantly significant materials was not only qualitatively novel, it was minute. And it was ultimately recognized to be three to six orders of magnitude below what had been admitted as relevant before. This descent into smaller orders of magnitude was but another instance of the direction taken in many of the sister sciences and probably received unconscious sanction from these trends. Thus, to name a few of these: morphology has used the microscope, light and electron, for its ends; physics has pursued the ever-smaller particles into the heart of the atom itself; and genetics did not rest until it came to a submicroscopic world of hydrogen bonds between certain special atoms in the special geometry of the double helix. The discoveries of 1913 in Madison were of a piece with a new world of science. As Kuhn has said [1, p. 110], "... paradigm changes do cause scientists to see the world of their research engagement differently. In so far as their only recourse to that world is through what they see and do, we may want to say that after a revolution scientists are responding to a different world." After 1913, I submit, it was a different world indeed.

But here I must end. For the news of the new paradigm of 1913 is no longer news. Worse, the real news, in my view, is that the paradigm of 1913 has become exhausted. The speed of discoveries of new qualitative entities in the field of micronutrients has slowed to a snail's pace and may have stopped altogether. The last important discovery of a new vitamin occurred inr!948 with the discovery of the chemical nature of vitamin B-12. That is more than 3 decades ago. This is not to say that nutritional scientists have not been busy. Much is to be learned about the function, the molecular roles, of the nutrients we know. And this is legitimate and should be done. What I am drawing attention to and labeling an exhausted paradigm is a paradigm that no longer casts up a continual array of new items, new components of the world of foodstuffs supporting the life of animals, and especially humans. As a graduate student here in the late 1930s it seemed as if this array of unknown and chemically undescribed items would stretch out in time longer than any of our professional lives could contemplate. But within a decade the list seemingly came to an end. Now what?

But this is the crisis that Kuhn warns us is the fate of all paradigms, to become exhausted as tools for discovery, sooner or later. We need a new Babcock, a new iconoclast, who will warn the onlookers at the parade that, indeed, the passing emperor has no clothes. And with the ground cleared and the shibboleths discarded, we need a new McCollum to point the way to a new paradigm.

Having said all this, and made bold by my personal ties as an inheritor of the Babcock-McCollum tradition, let me offer, very tentatively, one element that I think is bound to be a feature of the new paradigm. I can suggest it in a single word—disaggregation. What do I mean by that? I mean that, implicit in the laboratory rat model, and hidden in the simplistic assumption that a rat is a rat is a rat, is a tangle of rat genetics. Of this tangle we really know very little. If we now assume—and I think this assumption is defensible—that rat phenotypes are achieved by interaction of rat genotypes with the environment, and if nutrition is the richest and most intimate part of that environment, then disaggregating the rat genotype (or that of any experimental animal, for that matter) will fine-tune the rat paradigm into new responsiveness, a continuum that will bring to light new items and relationships of the nutritional world.

The consequences of disaggregation are obvious. Nutritional statements will become statements linked to specific genotypes. It is no accident that, in the current obeisance to reductionism, in some universities it has become necessary to prefix some departmental names with the word "organismic," to remind the listener or reader that what is really at stake is not molecules but live, growing, reproducing beings. Biology is in need of being reminded of that, and a science of nutrition is in similar need. The fundamental lesson of Madison, in 1913, was the discernment of the proper use of experimental animals as detectors of the fine structure of the nutritional environment. That lesson I do not propose to allow to be forgotten.

The reduction of life to the spin of electrons but leaves us staring at spinning electrons and completely at a loss as to what to do about them. The science of nutrition, on the other hand, has goals linked to the human condition, a condition that leaves us all dependent on a thin layer of life on a very lonely planet. I am confident that a science of nutrition will, in the fullness of time, find fresh things to say about that dependency. We must strive for new beginnings, and the centennial of the Department of Agricultural Chemistry at Madison is a reminder to nutritionists and biochemists of their beginnings and urges them to forge anew the mission that began there a century ago.

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