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Rats, Fats, and History*

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All have heard the phrase "bringing coals to Newcastle." The remark is intended to convey the sense of a useless performance, of the needless struggle to do what has already been done and, to render a final judgment, that the whole exercise is a waste of time.

My assignment has been to come to Madison and to speak to the subject "Fat-Soluble Vitamins." Before I am smudged with coal dust, and have confused the Yahara River with the Tyne, I think I owe you a few words of explanation.

Many here in the audience are residents of Madison, and it goes almost without saying that those of us who have been invited back for this centennial celebration were once Madisonians, at least for a while. In my particular instance I left Madison in August 1939, just 44 years ago. I fully expected to return to the department after a fellowship year at Cambridge, but events such as World War II took over. I think I am speaking for many when I recall that when I left, having spent both undergraduate and graduate years in Madison, I found it difficult to imagine a more desirable place to live than here. In due time, however, I found that it wasn't necessary to freeze in winter and boil in summer, that there were other places and other climes. But Madison always has a permanent and nostalgic charm for us expatriates; a charm that has more to do with our experiences here, than with, say, the eclectic architecture of a campus that never quite remembered what it had in mind.

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No, I prefer to think of the Madison experience much as Thoreau thought of his life on Walden Pond. He lived there only a bit over two years, and when he left and was seen again on the streets of Concord, he was accused by an acquaintance of having, by his departure, given lie to his touting of the life at Walden as the very best that a man might do. Thoreau's answer was, as is mine, "I have many lives to live."

In returning to Madison, then, we might be expected to bring some small contribution from our intervening years, even as we respond to our respective assignments. I found that my assignment to discuss the fat soluble vitamins allowed me a certain freedom of selection in what I might be reasonably expected to say. Here, then, is the framework of what I have to say.

Although the founding date of the Department of Agricultural Chemistry of the University of Wisconsin is given as 1883, I shall leave those earlier days to others and focus my remarks on the year 1913. That is not 100 years ago, but it is a respectable 70, or the proverbial three score and ten. It also happens to be my own age, and it is the year when the words "Agricultural Chemistry" were inscribed in the stone lintel over the entrance door to the first building to bear the name on this campus. If you care to look you will find it still there.

Why I chose 1913 will become clearer a bit later, but now I will choose further and say that I will not, for this audience, bring coals, and I will not set forth the details of the fat-soluble vitamins, their biochemistry, physiology, or—God save the mark—their molecular biology. What I propose is to delineate, as best I can, the historical and philosophical roots of their discovery, and for this occasion, try to understand why the fat-soluble vitamins were discovered here in Madison; why it was in 1913; and how the people who did it came to do it just then. As you can now tell, absence from Madison has made me bolder, for I wince even now from what Professor Hart and Dr. Steenbock would say to him who would talk philosophy under this roof. I tried it once, and Dr. Steenbock advised me to "wait until you are older." I think I now qualify, and can come out of the philosophical closet.

Why Madison?

In thinking about the questions raised by recognition that a certain event—say, the discovery of vitamin A—took place not far from where I stand, is to link that unique event with specifications of time (1913) and place (Madison, Wisconsin). 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 can produce all of 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 metaphor, 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. And we are here today to celebrate our ties to that 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 (Kuhn, 1962).

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 A and D, 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, are busy with what he calls "normal science." This means getting on with solving the problems that are reared within a conceptual framework which 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, 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 is 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, followed 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 feedstuffs to provide information capable of predicting the ability of assembled rations to nourish farm animals. This failure had important and obvious economic consequence. 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 five years after the founding of the department here, 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 Experiment 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 (de Kruif, 1928) so there is no need to dwell on it. But two events occurred in the life of Babcock which, by hindsight, we can now see as forming the preconditions which led to the discovery of vitamins A and D. 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 and D was thus two-fold: 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 feedstuffs, 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 feedstuffs, and the struggle always was to devise the most nourishing and, simultaneously, the most economic combination. Chemical analysis of the separate feedstuffs 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 didn't 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 feedstuff 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—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 three 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. Dr. Babcock did not publish.

Six years later, in 1907, Babcock got his second chance, this time not with two cows but with sixteen. The results, the famous Research Bulletin #17 of the Wisconsin Agricultural Experiment Station, appeared four years later, in 1911 (Hart et al., 1911). 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, all familiar to this audience, showed that identical chemical analyses failed to predict identical 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. C. 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 E. V. McCollum. He has given us an autobiographical account (McCollum, 1964) 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.

E. B. 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 sixteen cows. It was an analytical treadmill and McCollum soon tired of it.

McCollum started work here 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; 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 light-hearted, 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 (McCollum, 1964).

> 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 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 the chemical methods 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 an 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 this department I think it is fair to say that E. V. 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 one 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 that 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 thirty-seven volumes of a German publication, Maly's *Jahresbericht uber 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 (McCollum, 1964), "From Maly's *Jahresbericht* 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 thirty-seven 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 (McCollum, 1964):

> 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. A whole new world of experimentation beckoned. Late in 1907 McCollum broached his idea to Professor 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 which 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, gave way to the endorsement of Babcock, and McCollum was on his way, tolerated if not whole-heartedly approved by his superiors. But when McCollum placed a requisition for two dollars' 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 $1200 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 make-shift cages, he approved an allocation of fifty dollars 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, 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 strategic necessity, of designing experimental diets from purified foodstuffs. Slowly it had to be learned that chemical purification, the elimination of confounding materials brought along from the natural sources of these materials, was the crux. For 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 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 will address the discovery of the first fat-soluble vitamin, vitamin A, momentarily; but it should not be lost upon 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,** two years after the watershed year of **1913,** and was restated more formally in **1925** (McCollum, **1957).** 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. 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 foostuffs for interpretation by standards accepted a priori, but chemistry was used 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 which, 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 dead certain that if favorable response occurred, then the important substance, or substances, were to be sought in the supplement. If the supplement was the hay stack, 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 which 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 which 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 (McCollum and Davis, 1913) 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 as to the nature of this difference was next resolved unambiguously when McCollum and Davis (McCollum and Davis, 1914) showed that the growth-promoting lipid was in the relatively small residue of the fat that was not saponifiable, "the nonsaponifiable 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 (McCollum, 1964), "We had discovered vitamin A."

The dam had been breached here in Madison in 1913, and the river of further successful investigations here 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 here 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 coworkers 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, we all know how Harry Steenbock traced the action of ultraviolet radiation in activating vitamin D precursors into antirachitic activity. The vitamin D story goes on in these laboratories even today. But it is not too early to discern the historical significance of the work here by DeLuca and his coworkers 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, as I am sure we will learn from other participants in this Centennial, 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 (DeLuca and Shapiro, 1981; Hennekens et al., 1982).

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 believe that the audience here at the Wisconsin Centennial would be ill-served if I did not digress to shed what light I can on the history of Marguerite Davis, who was McCollum's assistant and collaborator for seven years, from 1910 to her unexplained resignation in 1916, just before McCollum went to his new post at Johns Hopkins. During this period Davis was the junior coauthor with McCollum in the publication of ten research articles, nine of which appeared in the *Journal of Biological Chemistry.* For these facts, as well as others in the life of Miss Davis, I am indebted to Harry G. Day (Day, 1983), professor emeritus of chemistry, University of Indiana.

Marguerite 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 the Wisconsin story such as we are celebrating here, For Marguerite Davis was a Wisconsin native, born in Racine on September 16, 1888. She died in that city just two days after her 79th 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 then 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 here at Madison, she presented herself as a kind of freelance 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 speeded 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 if 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 ten, 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 here 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' 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 1840's. The home overlooked Lake Michigan and here Marguerite Davis lived out her days.

The history of Elmer Verner McCollum, his dedicated assistant, Marguerite Davis, and the fateful year of 1913 here at the Department of Agricultural Chemistry, all bear witness to the revolution in nutritional research that was born here. 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 cargo, the 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 four decades. The lifetimes and the successful careers of many who are celebrants here are but the fruits of that new paradigm.

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 quantification. 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 here in Madison were of a piece with a new world of science. As Kuhn has said (1962), ". . . . paradigm changes do cause scientists to see the world of their research engagement differently. Insofar 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 now 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 pace 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 in 1948 with the discovery of the chemical nature of vitamin B_{12}. That is more than three 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 1930's 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 with 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 paradigm acoming. 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 of any experimental animal, for that matter) will multiply 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 let you forget.

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 it. The science of nutrition has goals linked to the human condition, a condition which 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 this Centennial strikes me as a good time to remind you of this, and urge you to get on with the mission that began here a century ago.

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