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# Deuterium as a Probe of the Boundaries between Physics, Chemistry and Biochemistry

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Radioisotopes were the first type of isotope to be found in the early 20<sup>th</sup> century, and ever since they have attracted the lion's share of attention from both scientists and lay people. This includes historians of science, who, in comparison, have had comparatively little to say about the significance of *stable* isotopes.<sup>1</sup> A notable exception has been Robert Kohler, who examined the impact of deuterium and other stable isotopes on the investigation of intermediary metabolism.<sup>2</sup> Kohler's narrative integrates the numerous institutional, social, economic and scientific factors that shaped this development, but doesn't discuss the actual techniques of isotope detection and measurement, a topic that has been neglected in the historical literature. The aim in this paper is to argue that the subject has something to tell us about disciplinary boundaries and about their permeability.

## The Importance of Deuterium

The study of experimental techniques is as important as the investigation of conceptual content for tracing the evolution of fault lines between disciplines.<sup>3</sup> The early history of deuterium provides an illustrative case study. Discovered in late 1931, this heavy isotope of hydrogen (<sup>2</sup>H<sub>1</sub> or D) was immediately an object of intense interest on the part of both chemists and physicists, and shortly thereafter it proved to be a uniquely powerful tool in biochemistry.<sup>4</sup> However, the experimental and theoretical techniques used to manipulate this nuclide, and the uses to which it was put, varied markedly in ways that initially reinforced but later undermined the distinctions between disciplines.

The detection of deuterium by H. C. Urey<sup>5</sup> and his colleagues<sup>6</sup> was received in the chemical community with great fanfare. *Industrial and Engineering Chemistry* asserted, in its lead editorial for 1934, "The importance of the discovery and pre-

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paration of the isotope of hydrogen, named 'deuterium', may be far greater than that of most elements. It seems certain that in years to come it will be ranked among the great discoveries in science. It is the starting point in developing a far-reaching new field in chemistry".<sup>7</sup> It is not difficult to understand the enthusiasm that greeted this new arrival. Most of the then known isotopes belonged to elements that played little or no role in most chemists' work, especially that of organic chemists and biochemists. Hydrogen, on the other hand, is ubiquitous in the compounds dealt with by these scientists. So the substitution of deuterium for the light hydrogen isotope, protium ( $^1\text{H}_1$  or H), in organic compounds was expected to open an entirely new window on chemical properties and processes. Indeed, the large relative mass difference between the hydrogen isotopes (100%) led G. N. Lewis to assert that "the isotope of hydrogen is, beyond all others, of interest to chemists". He predicted that "it will be so different from common hydrogen that it will be regarded almost as a separate element", and noted that "If this is true, the organic chemistry of compounds containing the heavy isotope of hydrogen will be a fascinating study".<sup>8</sup> Lewis was not alone in placing the discovery of deuterium among the most significant contemporary achievements in science; the Nobel Committee awarded Urey the Chemistry Prize in 1934, less than three years after his first publication on deuterium.

### **The Detection and Determination of Deuterium**

Using emission spectroscopy, Urey had detected the heavy isotope in a sample of liquid hydrogen that had been concentrated by low temperature distillation. While this approach sufficed to confirm the presence of deuterium, it couldn't give an accurate estimate of its concentration. For that, Urey measured the refractive index of a sample of water obtained by oxidising a portion of the deuterium-containing sample.<sup>9</sup> As will be seen, the chemists and physicists who scrambled to exploit Urey's discovery divided according to their analytical techniques and objects of study; significantly, Urey himself published his spectroscopic results in the *Physical Review* and his refractive index work in the *Journal of the American Chemical Society*.

Urey's refractive index article was followed closely by G. N. Lewis's piece on the same topic.<sup>10</sup> Immediately after Urey's discovery of deuterium, Lewis had initiated a vigorous research program centered on the isolation and study of this isotope.<sup>11</sup> Among chemists, the principal approach to quantifying the amount of deuterium present in a substance was to oxidise the sample completely, thereby converting all of the hydrogen and deuterium to isotopically enriched water, and then

measuring its density. Just a few months after Urey's first paper appeared, Polanyi and Gilfillan described a micropycnometer that could measure densities of samples as small as  $10^{-5}$  mg.<sup>12</sup> With larger samples, densities could be determined to one ppm or less using the falling drop method, in which a drop of the sample is allowed to fall through a liquid of nearly identical density, the rate of fall being proportional to the deuterium content. As noted, the alternative was to measure the liquid's refractive index; by combining the data from the two measurements it was possible to calculate the content of both  $^{18}\text{O}$  and D.<sup>13</sup> As far as the conversion of a sample's hydrogen quantitatively to water was concerned, chemists had over a century's experience with combustion analysis, while accurate measurements of densities and refractive indices were also well established procedures in the chemists' arsenal.<sup>14</sup> Thus, the incorporation of deuterium, with all its investigative potential, into chemical practice was rendered almost painless by the fact that it could be accomplished using methods so familiar that many were routinely taught to students. Furthermore, these methods had theoretical as well as practical significance. For example, by treating deuterium as a distinct chemical species, its behavior could be brought under the aegis of equilibrium thermodynamics, an area in which Lewis was an acknowledged master.<sup>15</sup>

Lewis was also working on the separation of lithium isotopes, and his former graduate student, Jacob Bigeleisen, said of this project that Lewis and his co-worker used "nothing but simple chemistry for the enrichment process, the determination of the relative atomic weights for analytical purposes, a mastery of chemistry, and hard work".<sup>16</sup> Much the same could have been said of his experiments with deuterium. Lewis's commitment to pursuing his deuterium work within a chemical framework is captured clearly in another observation by Bigeleisen:

"No molecular theory of the condensed phase isotope effect existed at that time [1934]. In fact, it was the absence of such a theory... that made these studies interesting to Lewis. In his Madrid lecture Lewis states, '...it is often these very cases which defy the analysis of mathematical physics that are of the most interest to chemists'".<sup>17</sup>

It is likely that Lewis's chemical contemporaries shared these sentiments as fully as they embraced his techniques.

The natural abundance of deuterium in hydrogen is only 0.2 atom-percent, insufficient for detection with the techniques available in the 1930s. Enrichment was therefore mandatory. Urey's coworkers initially accomplished this by distilling six liters of liquid hydrogen near its triple point ( $\sim 14$  K) and then examining the residual few mL, but this was not a very suitable process for isolating large quanti-

ties of the pure isotope. For this, Urey, Lewis and others chose electrolysis of water, another technique with a long history in chemistry.<sup>18</sup>

No matter what the origin of the deuterium, chemists overwhelmingly chose to monitor it via the density and/or refractive index of the derived water. What other parameters might they have availed themselves of? The measurement of nuclear magnetic moments was experimentally quite difficult and not then feasible for condensed phases.<sup>19</sup> Spectroscopic studies of deuterium were virtually all carried out in the gas phase and focused on the energy levels of atomic and molecular hydrogen (H, H<sub>2</sub>) and deuterium (D, D<sub>2</sub>).<sup>20</sup> That left only the mass to charge ratio as a characteristic that could be used for identifying and quantifying isotopes; in other words, mass spectrometry. Commercial mass spectrometers were not available and the home-made ones constructed by physicists required constant attention due to a host of problems unfamiliar to most chemists.<sup>21</sup> Moreover, these spectrometers were designed primarily to give accurate values of nuclear masses, not their abundances.<sup>22</sup> Finally, water ranks as one of the least amenable compounds for mass spectrometric analysis because of the great difficulty involved in removing residual water from the spectrometer. Thus, physicists and chemists were clearly divided not only by the purposes for which they used deuterium but as well by the experimental methods employed in its study. For physicists the analytical species of interest were atomic and molecular deuterium (D, D<sub>2</sub>), while for chemists it was partially deuterated water.

These two distinct analytical traditions eventually melded together in biochemistry. As Kohler has shown, Schoenheimer at Columbia became convinced of the revolutionary possibilities that deuterium held out in the study of intermediary metabolism. Before the advent of isotopic tracers, metabolic studies depended on adding some compound to an organism's diet, isolating the excreted products and concluding that the second had arisen somehow from the first. Schoenheimer likened this approach to putting a penny in a vending machine, taking out a piece of chocolate and assuming that the penny had been turned into chocolate.<sup>23</sup> In a less jocular assessment, he noted that:

“The study of the metabolism of substances which occur in nature in large amounts and are continually synthesized and destroyed in the animal body presents almost insuperable difficulties. If substances such as naturally fatty acids, amino acids, etc., are administered to an animal, we lose track of them the moment they enter the body, since they are mixed with the same substances already present... The difficulty in following physiological substances in the course of their transportation in the body, and their conversion into other substances, accounts for our ignorance with respect to many of the most fundamental ques-

tions concerning intermediate metabolism. The solution of these problems will be possible only when direct methods for tracing such substances are available".<sup>24</sup>

Overnight, the incorporation of isotopic tracers held out the promise of a degree of certainty in these studies that had been only dreamed of before. In Schoenheimer's words, the possibilities "[appear] to be almost unlimited".<sup>25</sup> In actuality, this new application of deuterium came to pass so soon only because David Rittenberg, one of Urey's PhDs, could not find employment as a physical chemist and went to work with Schoenheimer. It was his exploration and refinement of analytical techniques that allowed the promise of isotopic tracers in metabolism studies to be realised.<sup>26</sup>

Rittenberg initially used the same analytical techniques that all other chemists did, in which samples were burned and the deuterium content calculated from the density and/or refractive index of the resulting water. The results were amazingly accurate but the purification procedures, for both equipment and samples, bordered on the excruciating.<sup>27</sup> As a result, Rittenberg began to experiment with alternate analytical pathways because the nature of the metabolism studies imposed additional restrictions on the experimenters. In particular, sample sizes were often quite small and large numbers of analyses were needed. Rittenberg began to utilise a reaction that had been studied earlier by both Polanyi and Farkas, in which the partially deuterated water underwent catalysed exchange with molecular hydrogen, and the resulting partially deuterated hydrogen then became the analytical target.<sup>28</sup> At first, Rittenberg determined its deuterium content by microthermal conductivity, a procedure that had also been worked out by his predecessors. However, he had already had experience with mass spectrometry while working with Urey, and eventually built a mass spectrometer to analyse the hydrogen/deuterium gas mixture ( $H_2/HD/D_2$ ), which was a comparatively unproblematic procedure. As he noted in 1942, determining isotopic composition with a mass spectrometer was not as accurate as determining it from the density of the water. On the other hand, the mass spectrometric method was not affected by impurities, while with density measurements, "the limiting factor is not the determination of the density of water but its purification".<sup>29</sup> Furthermore, when fully refined, the combined combustion/mass spectrometric method could yield duplicate analyses on 3-5 mg samples of water in 40 minutes.

The push to develop mass spectrometric techniques was given additional impetus by the desire of biochemists to use doubly labeled substrates, such as <sup>15</sup>N-enriched deuterated amino acids.<sup>30</sup> The nitrogen in the sample could be converted to nitrogen gas by known reactions and also analysed mass spectrometrically. Thus, a combination of the enormous potential of isotopic tracers for biochemistry and

the exigencies imposed by the nature of the biochemical experiments led to a fusion of the techniques and approaches of physicists and chemists.

After World War II, biochemists increasingly turned away from stable isotopic tracers because of the availability of artificial radioisotopes such as tritium ( $^3\text{H}_1$  or T) and  $^{14}\text{C}$ , which could be easily tracked by liquid scintillation counting.<sup>31</sup> Chemists' allegiance to deuterium and other stable isotopes, by contrast, remained firmly entrenched. The large mass ratio of deuterium to protium was successfully exploited for mechanistic studies in the form of equilibrium and kinetic isotope effects.<sup>32</sup> It also prompted some striking speculations from Urey, who noted in his 1934 Willard Gibbs Medal address that:

“The differences are so great that, if deuterium had been present in a larger proportion in natural hydrogen, its effects could not have been overlooked. Many of our fundamental laws of chemistry could not have been established. It is difficult to estimate what the effects on the history of chemistry would have been. The development of chemistry as an exact science might have been greatly retarded. The atomic weight of hydrogen would not have been constant and perhaps the general acceptance of the atomic theory would have been delayed. On the other hand, the discovery of the isotopes of hydrogen might have been made much sooner, though what we could have done with them in the middle of the nineteenth century, I do not know”.<sup>33</sup>

When, in the 1950s, nuclear spin ceased to be the plaything of physicists alone and chemists embraced NMR, deuterium had a special role to play as a sort of virtual element, an absence rather than a presence, the antithesis of its shining career as a tracer.

## Notes

<sup>1</sup> A qualitative sense of historians' predilections can be gained by entering the Subject and Keyword search terms “radioactivity”, “radioisotope”, “stable isotope”, “deuterium”, etc in the History of Science, Technology and Medicine database.

<sup>2</sup> Robert E. Kohler, Jr., “Rudolf Schoenheimer, Isotopic Tracers, and Biochemistry in the 1930's”, *HSPS* 8 (1977): 257-89.

<sup>3</sup> Valuable discussions of the relationship between experimental practices are found in Doris T. Zallen, “Redrawing the Boundaries of Molecular Biology”, *J. Hist. Biol.* 26 (1993): 65-87, and Matthias Dörries, “Easy Transit: Crossing boundaries Between Physics and Chemistry in mid-Nineteenth Century France”, in *Making Space for Science: Territorial Themes in the Shaping of Knowledge*, ed. Crosbie Smith and Jon Agar (New York: St. Martin's, 1998), 246-62. Dörries offers a trenchant critique of the spatial metaphor in discussions of scientific boundaries.

<sup>4</sup>A bibliography published a little over a year after the first definitive identification of deuterium contained 109 entries: "Deuterium", *I&EC News Edition* 12 (1934): 11-12. The interest remained high, as shown by Alice H. Kimball, *Bibliography of Research on Heavy Hydrogen Compounds*, ed. Harold C. Urey and Isidor Kirschenbaum (New York: McGraw-Hill, 1949), which ran to 350 pages.

<sup>5</sup> For Urey, see James R. Arnold, Jacob Bigeleisen, and Clyde A. Hutchinson, Jr., "Harold Clayton Urey: April 29, 1893-January 5, 1981", *Biog. Mem. Nat. Acad. Sci.* 68 (1995): 363-412.

<sup>6</sup> Harold C. Urey, F. G. Brickwedde and G. M. Murphy, "A Hydrogen Isotope of Mass 2", *Physical Review* 39 (1932): 164-65; "A Hydrogen Isotope of Mass 2 and its Concentration", *Phys. Rev.* 40 (1932): 1-15.

<sup>7</sup> Harrison E. Howe, "The Editor's Page", *I&EC* 26 (1934): 1-2, on 1.

<sup>8</sup> Gilbert N. Lewis, "The Isotope of Hydrogen", *JACS* 55 (1933): 1297-98, on 1298.

<sup>9</sup> R. H. Crist, G. M. Murphy and Harold C. Urey, "The Isotopic Analysis of Water", *JACS* 55 (1933): 5060-61.

<sup>10</sup> Gilbert N. Lewis and Daniel B. Luten, Jr., "The Refractive Index of H<sub>2</sub>O<sup>18</sup>, and the Complete Isotopic Analysis of Water", *JACS* 55 (1933): 5061-62.

<sup>11</sup> Jacob Bigeleisen, "Gilbert N. Lewis and the Beginnings of Isotope Chemistry", *J. Chem. Ed.* 61 (1984): 108-16.

<sup>12</sup> E. S. Gilfillan and M. Polanyi, "Mikropyknometer zur Bestimmung von Verschiebungen im Isotopenverhältnis des Wassers", *Z. Phys. Chem. A* 166 (1933): 254-56.

<sup>13</sup> Lewis and Luten, "Refractive Index, 5062."

<sup>14</sup> Aaron J. Ihde, *The Development of Modern Chemistry* (New York: Dover, 1984 [1970]), 175-79, 393.

<sup>15</sup> Gilbert Newton Lewis and Merle Randall, *Thermodynamics and the Free Energy of Chemical Substances* (New York: McGraw-Hill, 1923).

<sup>16</sup> Bigeleisen, "Gilbert N. Lewis", 111.

<sup>17</sup> Bigeleisen, "Gilbert N. Lewis", 112.

<sup>18</sup> Edward W. Washburn and Harold C. Urey, "Concentration of the H<sup>2</sup> Isotope of Hydrogen by Fractional Electrolysis of Water", *PNAS* 18 (1932): 496-98; Henry Eyring and Albert Sherman, "Theoretical Considerations Concerning the Separation of Isotopes", *J. Chem. Phys.* 1 (1933): 345-49; I. Laird Newell and J. B. Ficklen, "Concentration of the Heavy Hydrogen Isotope", *JACS* 55 (1933): 2167.

<sup>19</sup> Paul Forman, "Molecular Beam Measurements of Nuclear Moments before Magnetic Resonance. Part 1: I. I. Rabi and Deflecting Magnets to 1938", *Annals of Science* 55 (1998): 111-160.

<sup>20</sup> Ref. 6; David H. Rank, "The Isotope of Hydrogen in the Atomic Spectrum", *Phys. Rev.* 42 (1932): 446; Muriel F. Ashley, "The Band Spectrum of H<sup>1</sup>H<sup>2</sup>", *Phys. Rev.* 43 (1933): 770; Gilbert N. Lewis and Muriel F. Ashley, "The Spin of the Hydrogen Isotope", *Phys. Rev.* 43 (1933): 837.

<sup>21</sup> S. H. Bauer, "Mass Spectrometry in the Mid-1930's: Were Chemists Intrigued?" *J. Am. Soc. Mass Spect.* 12 (2001): 975-88.

<sup>22</sup> Kenneth T. Bainbridge, "The Isotopic Weight of H<sup>2</sup>", *Phys. Rev.* 42 (1932): 1-10; H. Lukanow and W. Schütze, "Ein Massenspektrograph nach der Parabelmethode mit großer Linienstärke", *Z. f. Physik* 82 (1933): 610-19. John A. Hipple noted that "Very early in the development of instruments for mass analysis of ions there occurred a natural diversion of the work into two channels. Those physicists interested in the accurate measurement of the masses of the elements developed instruments with very narrow slits and photographic recording .... [those] more interested in the accurate measurement of the relative amounts of the ions of different masses pre-



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sent worked with instruments of fairly wide slits and measured the ion current electrically”: “Gas Analysis with the Mass Spectrometer”, *J. Appl. Phys.* 13 (1942): 551-59, on 551.

<sup>23</sup> Mildred Cohn, “Some Early Tracer Experiments with Stable Isotopes”, *Protein Science* 4 (1995): 2444-47, on 2444.

<sup>24</sup> Rudolf Schoenheimer and D. Rittenberg, “Deuterium as an Indicator in the Study of Intermediary Metabolism. I”, *J. Biol. Chem.* 111 (1935): 163-68, on 163.

<sup>25</sup> Rudolf Schoenheimer and David Rittenberg, “Deuterium as an Indicator in the Study of Intermediary Metabolism”, *Science* 82 (1935): 156-57, on 157.

<sup>26</sup> D. Rittenberg and Rudolf Schoenheimer, “Deuterium as an Indicator in the Study of Intermediary Metabolism. II. Methods”, *J. Biol. Chem.* 111 (1935): 169-74; Jack Graff and David Rittenberg, “Microdetermination of Deuterium in Organic Compounds”, *Anal. Chem.* 24 (1952): 878-81; David Shemin and Ronald Bentley, “David Rittenberg: November 11, 1906-January 24, 1970”, *Biog. Mem. Nat. Acad. Sci.* 80 (2001): 257-74. In my view, Kohler (“Rudolf Schonheimer”) does not give sufficient weight to the role played by Rittenberg.

<sup>27</sup> Albert S. Keston, D. Rittenberg, and Rudolf Schoenheimer, “Determination of Deuterium in Organic Compounds”, *J. Biol. Chem.* 122 (1937) 227-37.

<sup>28</sup> J. Horiuti and M. Polanyi, “A Catalyzed Reaction of Hydrogen with Water”, *Nature* 132 (1933): 819; Adalbert Farkas, “A Method of Analysis of Heavy Water”, *Trans. Farad. Soc.* 32 (1936): 413-15.

<sup>29</sup> D. Rittenberg, “Some Applications of Mass Spectrometric Analysis to Chemistry”, *J. Appl. Phys.* 13 (1942): 561-69, on 561.

<sup>30</sup> Rudolf Schoenheimer, D. Rittenberg, M. Fox, Albert S. Keston and Sarah Ratner, “The Nitrogen Isotope ( $N^{15}$ ) as a Tool in the Study of the Intermediary Metabolism of Nitrogenous Compounds”, *JACS* 59 (1937): 1768; D. Rittenberg, Albert S. Keston, F. Rosebury and Rudolf Schoenheimer, “Studies in Protein Metabolism. II. The Determination of Nitrogen Isotopes in Organic Compounds”, *J. Biol. Chem.* 127 (1939): 291-99.

<sup>31</sup> Cohen, “Early Tracer Experiments”, 2447.

<sup>32</sup> Kenneth B. Wiberg, “The Deuterium Isotope Effect”, *Chem. Rev.* 55 (1955): 713-43.

<sup>33</sup> Harold C. Urey, “Significance of the Hydrogen Isotopes”, *I&EC* 26 (1934): 803-06, on 805.