

## THE ORIGIN OF THE WORD PROTEIN\*

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The word protein first appeared in scientific literature in 1838. It was used by Mulder as the designation of the complex radical which he thought to be combined with sulfur and phosphorus in the proteins as they occur in nature, and it has been commonly assumed that he himself originated the new term. That this is incorrect has recently been pointed out by Sir Harold Hartley<sup>1,2</sup> who, in the course of preparing an address commemorating the centenary of the death of Berzelius, found that Berzelius had suggested the word protein to Mulder in a letter written from Stockholm on July 10, 1838.<sup>3</sup>

Inasmuch as the correct origin of this word has been almost universally overlooked, the sequence of events which led to its publication may be of interest.

Mulder's investigations of proteins were begun in 1835 with chemical analyses of silk<sup>4</sup> and were soon extended to include fibrin, serum and egg albumin, gelatin, and a preparation of what is today known as wheat glutenin, together with various products derived from these substances by the action of acids and alkalies. Certain apparent regularities in the ultimate composition of the preparations convinced him of the presence in each of them of what contemporary chemical theory regarded as an oxidized basic radical which combined in simple ratios with sulfur and phosphorus to give the substances as they are found in nature. The name "protein," derived from the Greek adjective *πρωτεῖος*, meaning of the first rank or position, was given to this radical.

Mulder was convinced of the importance of these results and took what today seem rather extreme steps to provide for their wide dissemination. Two papers were published in journals of which he was himself an editor. In one of these, *Natuur- en scheikundig Archief*, his account<sup>5</sup> appears in volume 6 under the title "Over Proteine en hare Verbindingen en Ontledingsproducten" and runs from pages 87 to 162. A briefer article was

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*Received for publication February 11, 1950.*

printed in the recently established semi-monthly *Bulletin des sciences physiques et naturelles en Néerlande* where it is to be found in the issue dated July 30, 1838, in volume 1, page 104, under the title "Sur le composition de quelques substances animales." \* \*

Mulder also wrote a letter to Liebig † giving an outline of his analytical results and views, and the substance of this letter, with the notation "*aus einem Briefe an J.L.*," was published in *Annalen*, volume 28, page 73, in 1838. † In addition, the *Bulletin* paper was reprinted in German translation in the *Journal für praktische Chemie*, volume 16, pages 129 to 152, in 1839. †

In each of these papers, a statement is given of the derivation of the term protein. The sentence in the *Archief* paper may be roughly translated, "When all that has been described above is considered, it is clear that there is present in plant albumin, ‡ and in the animal albumin of silk, of eggs, of blood serum, as well as in blood fibrin, a substance common to all that we designate *protein* from *πρωτεϊος*, *primarius*, which is combined with sulfur and phosphorus in egg white and fibrin. . . . This is the foodstuff of the whole animal kingdom and is probably formed only by plants." In the *Bulletin* paper, the analogous phrase is "*pourrait se nommer Proteine de πρωτεϊος, primarius*," and, in its German translation in the *Journal für praktische Chemie*, this appears, "*könnte Protein von πρωτεϊος, primarius, genannt werden*." Later in the same paper, there occurs the sentence, "*Es wird aber nicht ohne Nutzen sein, die Untersuchungen des Körpers, den ich Protein genannt habe, noch weiter zu verfolgen*."

The internal evidence of the several papers, especially the use of the first personal pronouns, has seemed to most students of the matter (e.g., Vickery<sup>9</sup>) to point unmistakably to the conclusion that Mulder himself

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\* These extremely rare journals were short-lived; only six volumes of the *Archief* (1833-1838) and three of the *Bulletin* (1838-1840) were published. There is a file of the *Archief* in the Library of the U. S. Patent office and one at the Massachusetts Institute of Technology and of the *Bulletin* in the Library of Congress.

† A single number of the *Bulletin* contained 8 pages; Mulder's paper began on p. 104 of the issue (No. 13) dated July 15, 1838; this page carries the title and the first two paragraphs, and the date of issue accounts for the fact that the title does not contain the word protein as the title of the *Archief* paper does. The issue of July 30 (No. 14), pages 105 to 112 inclusive, contained more of the paper, and it is in these pages that the definition of protein is first given. The paper was completed in the issue (No. 15) dated August 15, 1838.

‡ This letter to Liebig was mentioned by Mulder in a letter to Berzelius dated August 17, 1838. He added that, "according to custom, it will be printed in the *Annalen*."

§ The "plant albumin" to which he referred was a preparation of wheat glutenin obtained from gluten, after the gliadin had been removed by extraction with alcohol according to Beccari's technique, by solution in potassium carbonate and precipitation with acetic acid.

originated the term protein, and Sir Harold Hartley's discovery is therefore a matter of considerable surprise.

The source of his information was the collected letters of Berzelius published by H. G. Söderbaum in Uppsala in 1916.\*<sup>8</sup> Volume 5 contains the correspondence between Mulder and Berzelius from 1834 to 1847. In the spring and early summer of 1838, Mulder had described his analytical studies of the proteins and had given his reasons for supposing that there is a radical common to all of these substances. On July 10, 1838, Berzelius wrote Mulder a long letter which contains the following sentences :

“Or je présume que l'oxyde organique, qui est la base de la fibrine et de l'albumine (et auquel il faut donner un nom particulier p. ex. protéine) est composé d'un radical ternaire, combiné avec de l'oxygène dans quelqu'un de ses rapports simple que la nature inorganique nous présente.”

and, later in the same letter,

“Le nom protéine que je vous propose pour l'oxyde organique de la fibrine et de l'albumine, je voulais le dériver de *πρωτειος*, parce qu'il paraît être la substance primitive ou principale de la nutrition animale que les plantes préparent pour les herbivores et que ceux-ci fournissent ensuite aux carnassiers. En dérivant le nom du mot grec pour la fibre, il serait moins convenable, puisque l'oxyde organique est la base aussi de l'albumine et probablement de la matière colorante, ainsi que d'autres encore.”

In his answer to this letter on August 17, 1838, Mulder makes frequent use of the word protein although he did not specifically acknowledge Berzelius' suggestion.

Why, then, if Mulder owed to Berzelius the suggestion of the word protein,† did he use the first personal pronoun in connection with it in several of his publications? The most likely explanation of this is that, in both the *Archief* and the *Bulletin* papers, Mulder in the first sentences acknowledged his general indebtedness to Berzelius for helpful comments and advice. Mulder was, at this time thirty-five years old (Berzelius was fifty-nine) and had only recently begun to make himself known for his

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\* There is a complete set of Berzelius' letters<sup>8</sup> in the Historical Library of Yale University School of Medicine.

† Mulder had not asked Berzelius to suggest a name, but in a letter of March 29, 1838 he refers to “*les substances animales sans soufre et sans phosphore*” which combine with sulfur and phosphorus to form egg and serum albumin. Berzelius' suggestion was thus an attempt to provide a less awkward means of expression. He chose a Greek root which referred to its fundamental nature in nutrition in preference to one which referred to a property (i.e., fibrous nature) possessed only by certain individual substances. “*La matière colorante*” was hemoglobin.

chemical investigations. His correspondence with Berzelius, which had begun in 1834 over the matter of preparing a translation into Dutch of Berzelius' *Traité de Chimie*, had, by 1838, become voluminous. It was carried on in terms of the warmest admiration on his side and in a spirit of kindly helpfulness on that of Berzelius. In Söderbaum's phrase,<sup>8</sup> Mulder became a "corresponding disciple" of Berzelius, and the relationship continued, with every evidence of increasing mutual esteem and intimacy, until Berzelius' death in 1848.

Berzelius had for many years been the international authority for new chemical words; cystine and glycine are two examples in the amino acid field, and catalysis and isomerism are others which illustrate his genius even better. The word protein was not itself the significant point to Mulder, and Berzelius himself laid no unusual stress on it; he merely said it is necessary to have a name. That he felt no strong proprietary rights is plain from his report for 1838 in the *Jahresbericht*<sup>10</sup> where he writes, "Mulder names the organic substance, that is the chief component of fibrin and albumin, protein from *πρωτεϊνω*,\* I take the first place." The word was a convenient one to express the fundamental idea Mulder was trying to convey and, at a time when new terms were frequently being introduced into chemistry, there did not seem to be any necessity to emphasize the precise origin of this one. Certainly, neither Mulder nor Berzelius could have had any clear idea of the importance it would assume after its connotation had been broadened and its meaning redefined as a result of the work of Liebig and the later generations of protein chemists. Wöhler, however, came to appreciate its value, for he wrote to Liebig<sup>11</sup> on February 19, 1848, at the height of the polemic with Mulder and in an effort to prevail upon Liebig to modify the asperity of his share in the discussion, that all of the personalities might well be overlooked in view of the fact that science had been enriched by the useful and appropriate word protein.

It is difficult to decide the exact date on which the new term was first published. Berzelius wrote his letter from Stockholm on July 10, 1838. Mulder at Rotterdam first employed the word in his paper in the issue of the *Bulletin* bearing the date July 30, 1838. Early in the paper is the statement that the author merely proposes to give a summary of his results and that the reader may consult the *Archief*, volume 6, for full details. This implies that the *Archief* paper, the title of which contains the word protein, was written before the paper in the *Bulletin*. The *Archief* paper is 75 pages

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\* In this instance, Berzelius employed the Greek verb as the root; previously he had suggested the adjectival form.

long and the *Bulletin* paper, in its German translation, 23 pages. It is almost incredible that Mulder could have written both of them between the receipt of Berzelius' letter of July 10th and the printing of the issue of the *Bulletin* dated July 30, and, in fact, there is no reason to assume that he did. It seems clear, from what Mulder wrote to Berzelius earlier in 1838, that his ideas on what came to be known as the "protein" hypothesis matured during the summer, and it is quite possible that he wrote much of the long *Archief* paper before he received Berzelius' letter. Save for the title, the word protein first occurs on page 128, rather more than halfway through. However, it is used at least once on no less than eighteen of the subsequent pages. This portion of the text must therefore have been written after the receipt of Berzelius' letter, and Mulder obviously wrote the title afterwards.

The *Bulletin* paper is, in effect, a condensation of a considerable part of the *Archief* paper. It is organized on the same plan; selected data are set forth in the first ten pages in support of the hypothesis that there is a radical common to several, at least, of the better known albuminous substances; the term protein is then defined in the language quoted above and is used on the next two pages several times. It does not occur again until the author mentions "proteinsulfuric acid" on the last two pages. In the *Journal für praktische Chemie* translation,<sup>8</sup> the translator added a note that the subject is "to be continued," and there are subsequent short papers in volume 16, one dealing with leucine and glycine<sup>12</sup> and another with "xanthoproteic acid,"<sup>13</sup> a term newly coined by Mulder for the "yellow acid" of Fourcroy and Vauquelin. Both of these subjects are discussed in the long *Archief* paper and also in separate short articles in the *Bulletin*.<sup>14</sup>

Little can be concluded from this except that the first few pages of the *Bulletin* paper *could* have been written before the receipt of Berzelius' letter. However, the general impression given is that most of the text was drafted after this letter reached Mulder. Accordingly, it would seem that the *Archief* paper was, for the most part, prepared before the *Bulletin* paper and it appears to be the first in which the term "protein" was used. Whether volume 6 of the *Archief* came from the printer in advance of the semi-monthly number of the *Bulletin* which bears the date July 30, 1838, remains in question.

There is some evidence on the time of appearance of the papers in the correspondence between Berzelius and Mulder. On March 29, 1838, Mulder wrote that "five numbers of the *Bulletin* and one number of the *Archief*, number 4, the last of 1837" had recently been sent. The *Archief* was apparently issued in four parts per year. On November 24, 1838, he

mentioned that he had sent "several numbers of the *Bulletin* and numbers one and two of the *Archief*" a short time previously. The paper "Over Protein" must have been included in these numbers of the *Archief*, for Mulder asked Berzelius, in a letter of January 8, 1839, to refer to pages 130 and 141 of the last number of the *Archief*, "which you have doubtless received."

The *Archief* paper was thus certainly in print in November 1838, and, since the *Bulletin* paper begins on page 104 and at least five numbers of this journal had been sent to Berzelius early in the year, there seems little doubt that this paper was also included in the package sent to Berzelius in November. However, this sheds little light upon which of the two papers became available to the public first.

One further point in connection with the discovery of the Berzelius letter should be emphasized because of its later importance in protein chemistry. This is the statement by Berzelius that protein (i.e., the radical) is the fundamental substance in nutrition and is synthesized by plants "*pour les herbivores et que ceux-ci fournissent ensuite aux carnassiers.*" Mulder repeated this idea, as is shown in the quotation from the *Archief* paper above, and enlarged on it to some extent both in this and in the *Bulletin* paper.

Liebig, a few years later, after he had, with his students, investigated the ultimate composition of several animal and plant proteins, became convinced of the essential identity of plant and animal proteins of corresponding solubility, and on June 28, 1841<sup>11</sup> he wrote to Wöhler: "We now have a complete analogy; we have plant albumin, plant fibrin, and plant casein all identical with each other and with the animal proteins that bear the same name. One can assert that the animal organism contributes merely the form of its blood." Without acknowledgment to Mulder, and still less to Berzelius, of whose statement he was doubtless unaware, Liebig pursued the implications of this idea. The doctrine that there are only four fundamental proteins in nature, namely, albumin, fibrin, casein, and gelatin, was enunciated<sup>12</sup> and, although the work of Ritthausen in the later decades of the century demonstrated it to be a gross over-simplification, this doctrine dominated the early years of protein chemistry and was finally refuted only in the first decade of the present century, largely through the work in this country of Osborne and his collaborators, especially Wells, who first demonstrated the complete specificity of the proteins of plant seeds. To the early workers, however, who had no means of estimating their molecular weight, proteins were relatively simple organic compounds which passed

from the plant into the animal metabolism with only minor change. The true complexity of the protein molecule has been fully appreciated only during the past few decades.

Berzelius' two contributions, the name and the notion of the fundamental role of the plant in protein metabolism, have undergone great modifications in the past century. Protein chemists may still, however, marvel at the genius which grasped the essential fact that the proteins occupy the first place in animal nutrition and thus in the truly essential affairs of mankind.

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