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Thomas Burr Osborne and Chemistry

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I count it an honor to appear before a meeting of the Division of the History of Chemistry. My talk will deal with the place of Thomas Burr Osborne in the historical development of protein chemistry (1). To begin with, I will describe briefly the state of that field in the late 1880s and the circumstances that brought Osborne into it. I will then try to summarize his work in relation to that of his principal contemporaries. Finally, I will speak about Osborne's qualities as a leader of his research group.

Osborne was a Connecticut Yankee who spent his entire life in New Haven. He was born there in 1859, went to Yale for his undergraduate and graduate studies, and studied chemistry there with William Gilbert Mixter. He was the only son of a prominent New Haven banker, who wanted young Osborne to join him in the Second National Bank, but at Yale he had become interested in analytical chemistry. A year after he had received his Ph.D., Osborne joined the staff of the Connecticut Agricultural Experiment Station, located in New Haven, where he headed the Biochemical Laboratory until 1928. He died in New Haven in the following year (2).

When Osborne came to the Station in 1886, its director was Samuel William Johnson [1830-1909], whose daughter Osborne married in the same year (3, 4). His first publications dealt with such matters as soil analysis, but in 1888, at the suggestion of his father-in- law, he turned to the chemistry of plant proteins, and published his first paper on the subject in 1891. The stimulus provided by Johnson was a consequence of the fact that he was an assiduous reader of the European literature on agricultural chemistry, and had come to admire the contributions of Heinrich Ritthausen [1826- 1912] (5). During the 1850s, Johnson had worked in Leipzig and had met Ritthausen at that time.

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Over a thirty-year period, beginning in 1862, Ritthausen published an extensive series of papers on the preparation and characterization of proteins from plant seeds. When he began this work, the only amino acids thought to be generally present in proteins were glycine, leucine, and tyrosine. Ritthausen added glutamic acid and aspartic acid to the list and showed that hydrolysates of proteins which Liebig had considered to

be identical substances differed greatly in their content of these amino acids. Along with others of his time, Ritthausen crystallized the seed globulins from several plants. The procedures were very simple: a sodium chloride solution was allowed to cool slowly, or dialyzed against water, whereupon well-developed crystals appeared. Some physiological chemists considered such crystalline proteins to be important. For example, in the 1887 (first) edition of his textbook, Gustav von Bunge wrote (6): "The analysis and investigation of the pure protein crystals and the various products of their cleavage should provide the groundwork for all of physiological chemistry." Apparently Johnson shared this view, but it should also be noted that his decision to encourage Osborne to engage in basic research on the chemistry of plant proteins reveals vision and courage in the face of the down-to-earth objectives of the Experiment Station, namely to provide reliable chemical analyses of commercial fertilizers.

At Johnson's suggestion, therefore, Osborne undertook to repeat and extend Ritthausen's studies, and between 1888 and 1901 Osborne's chief aim was the isolation and purification of the proteins of plant seeds. Beginning with oat seeds, from which he obtained crystalline avenin, he proceeded to study the proteins of over 30 different seeds; indeed, bottles containing samples of his preparations are still tucked away in the vault of the Johnson Laboratory at the Experiment Station. During this early phase of Osborne's work, his aim was to prepare what he considered to be pure proteins, and his principal criterion for purity was a reproducible elementary analysis for carbon, hydrogen, nitrogen, and sulfur. Accordingly, he set himself the task of checking the discordant reports in the earlier literature on the elementary composition of the seed proteins. As he expressed it in 1892 (7):

> The fact that these proteid substances can be artificially crystallized is not only interesting in itself, but is important as presumably furnishing a means for making preparations of undoubted purity which will afford a sure basis for further study of their properties. The contradictory statements made by various investigators, not only in regard to the properties and composition of these bodies but also in respect to the value of the methods of solution and separation which have been employed hitherto, render an exact knowledge of all the facts relating to these substances a matter of the highest scientific and practical importance.

Osborne's confidence in crystallization as a means of preparing pure proteins was not shared by some of his contemporaries. Thus, Louis Pasteur, who began his scientific work as a crystallographer, had stated in 1883 (8): "You know that the most complex molecules of plant chemistry are the albuminoid substances. You also know that these immediate principles have never been obtained in a crystalline state. May one add that apparently they cannot crystallize." Pasteur, by that time the great healer, apparently did not know of the work of Ritthausen and others on crystalline proteins from plant seeds, or chose to ignore it. After egg albumin had been crystallized by Franz Hofmeister [1850-1922] in 1889, the noted crystallographer Arthur Wichmann examined them, and wrote ten years later (9) that "There is scarcely a crystalline substance which, like a sponge, soaks up dissolved substances as does albumin." And in 1913, the great organic chemist Emil Fischer [1852-1919], of whom I shall have more to say shortly, wrote about crystalline proteins as follows (10): "... the existence of crystals does not in itself guarantee chemical individuality, since isomorphous mixtures may be involved, as is frequently the case in mineralogy for the silicates." Indeed, for most of the German organic chemists of Osborne's time, the proteins were included among the natural products which they chose to denote as *Schmiere*.

Also, at the turn of the century, leading biochemists had turned to the study of proteins as colloids, which Thomas Graham had defined as noncrystalline and nondiffusible substances, and they preferred to apply the new physical chemistry to the study of adsorption phenomena exhibited by proteins. It would seem, therefore, that Osborne chose to disregard prevalent opinion and, as a well-trained analytical chemist, to begin his work on proteins by single-mindedly pursuing his goal of purifying them by crystallization and of drawing conclusions about their identity or individuality from their elementary composition and their solubility properties.

In 1892, Osborne reported his findings on the crystalline globulins from six different kinds of seeds - Brazil-nut, oat-kernel, hemp-seed, castor-bean, squash-seed, and flax-seed. He concluded that the first two globulins are distinct proteins, and different from the other four, which appeared to him to be the same protein. Two years later, Osborne found the seed globulins from wheat, maize, and cotton to have the same elementary composition as the four seemingly identical proteins; and he considered the seven kinds of seeds to contain the same globulin, which he named "edestin." By 1903, however, he was obliged to revise this opinion, but in the mean- time he continued to amass data on many other seed proteins, including the alcohol-soluble prolamines such as zein and gliadin. In those intervening years, important advances had been made in protein chemistry,

and Osborne changed the direction of his research program accordingly.

The most important of these advances was the addition of many amino acids to the list of regular protein constituents. Those added between 1880 and 1903 included the basic amino acids lysine, arginine, and histidine, as well as phenylalanine, cystine, alanine, valine, isoleucine, proline, hydroxyproline, and tryptophan (11). In particular, the finding that the basic amino acids form sparingly-soluble salts with phosphotungstic acid led Walter Hausmann, a student in Hofmeister's laboratory, to develop in 1900 a method for the determination of the partition of the nitrogen in acid hydrolysates of proteins among the so-called ammonia-nitrogen, basic-nitrogen, and nonbasic nitrogen fractions. Osborne seized upon the Hausmann method, and in 1903 he reported that (12):

> We have found by its use that some of our preparations from different seeds which were so nearly alike in composition and reaction that no difference could be detected between them sufficient to warrant the conclusion that they were not the same chemical individual, yield such different proportions of nitrogen in the several forms of binding that there can be no longer any doubt that they are distinctly different substances. On the other hand, many preparations of different origin, which we have heretofore considered to be identical, have yielded the same proportion of the different forms of nitrogen and consequently our former opinion respecting the identity of these protein preparations is very greatly strengthened.

The next step in the development of Osborne's research program was his acceptance, in 1906, of the necessity of determining the amino acid composition of protein hydrolysates by means of the methods developed by Albrecht Kossel and Emil Fischer. In 1900, Kossel [1853-1927] had introduced a procedure for the quantitative estimation of the three basic amino acids, and in the following year Fischer described his so-called ester method for the separation of other amino acids present in acid hydrolysates of proteins. Because Fischer's name figures so prominently in the history of protein chemistry, I digress briefly from the account of Osborne's work.

By 1906, Fischer was widely regarded as the leading organic chemist of his time. He had received the Nobel Prize for Chemistry in 1902 for his outstanding achievements in the synthesis of sugars and purines; and, soon after entering the protein field in 1899, he had initiated an ambitious program to effect the synthesis of proteins. Apart from his lock-and-key analogy to describe the specificity of enzyme action, Fischer is perhaps best known for his synthesis of polypeptides. In December 1905, he wrote to his teacher Adolf von Baeyer as follows (13):

> On January 6th I will present a lecture at the Chemical Society summarizing my work on amino acids, polypeptides and proteins, and then early next year I will publish the collected papers in the form of a book. The material has grown splendidly and there is much detail in it. Recently I have also prepared the first crystalline hexapeptide and hope to obtain a matching octapeptide before Christmas. Then we should be close to the albumoses....My entire yearning is directed toward the first synthetic enzyme. If its preparation falls into my lap with the synthesis of a natural protein material, I will consider my mission fulfilled.

Although the accounts of Fischer's lecture in newspapers and in popular science journals encouraged the belief that the preparation of synthetic proteins was around the corner, by 1910 the enormous effort of his assistants had produced much less than he had hoped for, and his disappointment may be inferred from the fact that after that date there were no further experimental papers on peptide synthesis from his laboratory (14).

In Fischer's ester method, the mixture of amino acids in an acid hydrolysate of a protein was esterified with ethanol, alkali was added to generate the free esters, which were then extracted with ether. The ether extract was concentrated and subjected to fractional distillation under reduced pressure, and the esters in the individual fractions were converted to free amino acids, which were crystallized, weighed, and characterized. It surely must have been clear from the start that this method was not likely to give reliable quantitative data for the amino acid composition of proteins. Nevertheless, many protein preparations were analyzed in this way in Fischer's laboratory; and, apart from demonstrating the general occurrence of amino acids such as alanine or phenylalanine, three new protein constituents were found: proline, hydroxyproline, and diaminotrioxydodecanoic acid. Much of this work was done by Emil Abderhalden [1877-1950], who had come to Fischer's laboratory in 1902, after receiving his Dr.med. degree at Basle. Two years later, in a letter to a Berlin colleague, Fischer wrote (15):

> Because of his unusual capacity for work, in a short time Abderhalden has become so adept in the difficult methods of organic chemistry that I was able to accept him last fall as a collaborator in my private laboratory. I note that I had not dared to do this be-

> fore with a medical man. He is a good observer, and is an enemy of all superfluous hypotheses. Regrettably, biological chemistry is that part of our science in which imprecise and incomplete experiments are often heavily padded with the dazzling ornamentation of so-called ingenious reflections to producepretentious treatises. For this reason, people like Abderhalden are needed.

These opinions led Fischer to turn over to Abderhalden the succession of post-M.D. students who flocked to Fischer's laboratory at that time, and most of them worked under Abderhalden's direction on the application of the ester method to the analysis of a great variety of protein preparations, including plant proteins such as edestin and gliadin. However, Fischer's initial assessment of Abderhalden's chemical talent proved to be incorrect, for much of his work both as a member of Fischer's group and in later years as an independent investigator proved to be irreproducible. In particular, Fischer was obliged to withdraw diaminotrioxydodecanoic acid from his list of protein amino acids.

I now return to Osborne's work on proteins. By 1906, he had begun to receive financial support from the Carnegie Institution of Washington. This grant enabled him to hire more assistants and to purchase equipment for the preparation of the sizable amounts of proteins then needed for the analysis of their amino acid composition. Osborne applied the methods of Kossel and Fischer to the analysis of several seed proteins and also used other procedures to estimate the content of such components as tryptophan or sugars, which are destroyed upon acid hydrolysis. By 1908, these newer studies led Osborne to revise further his earlier views about the chemical individuality of the proteins he had purified (16):

> We are now well past the time when agreement in solubility, ultimate composition and color reactions are to be accepted as evidence of the identity of two preparations of protein....On the basis that agreement in ultimate composition affords no evidence of identity of two similar proteins, but that distinct and constant differences in composition are conclusive evidence that they are not alike, I ... have since subjected them to careful comparison in respect to their physical properties and the proportion of their decomposition products, so that those which are alike in their more apparent characters have been still further distinguished from one another.

Even though the use of the Fischer ester method had revealed new differences among the seed proteins, Osborne, as a well-trained analytical chemist, did not accept the limitations of the method, but proceeded to subject it to a more rigorous examination than that conducted in Fischer's laboratory, and improved it greatly (17). In this connection I cannot forbear from citing a passage from a letter from Fischer to Abderhalden in 1912 (18):

> I consider it likely that because of their greater wealth the Americans will beat us in several fields, and I have expressed this opinion at every opportunity. However, we can withstand this competition for a time because of our greater inventiveness and more distinguished individual achieve- ments. That the gentlemen in America are also rather presumptuous is nothing new to me, but one can defend oneself against this at a suitable opportunity. As soon as I find the time, I will discuss this question in a retrospect on chemical research on proteins during the past ten years.

Although his name is not mentioned, Osborne is the most likely candidate for Fischer's displeasure, as he was the leading protein chemist in the United States at that time.

Osborne's contributions to the analytical chemistry of proteins may perhaps best be illustrated by means of Table 1, taken from his review article in 1910 (19). The first column of numbers contains the data (grams per 100 g of protein) reported for zein by Ritthausen in 1872, the second column the data in 1903 of Langstein who used the Fischer ester method, and the third column the values given by Kossel and Kutscher in 1900 for tyrosine and the three basic amino acids. The fourth and fifth columns give the values reported from Osborne's laboratory in 1906 and 1910, respectively.

In addition to the contributions of Kossel, Hausmann, Fischer, and Abderhalden to the analytical chemistry of proteins, there was another series of developments which influenced the course of Osborne's research. The first was the discovery in 1901 by Otto Cohnheim [1873-1953] of the enzymatic conversion of peptones to amino acids by the intestinal mucosa. Before that time, many physiologists believed that, in the metabolic utilization of food proteins, the peptones formed by the action of pepsin and trypsin are taken up at the intestinal wall and converted there into blood proteins. The next blow to this doctrine came from Otto Loewi [1873-1961], who showed in 1902 that completely digested (peptone-free) pancreatic protein can replace intact protein in the animal diet. Osborne appears to have recognized at once the importance of these findings, for in 1903 he wrote (20): "The animal...can synthesize protein from a mixture of the crystallizable products produced by the decomposition of proteins." However, he did not pursue the consequences of this idea until 1909, when he and Lafayette Benedict Mendel

Table 1. Products of the Hydrolysis of Zein

Component	Ritthausen (1872)	Langstein (1903)	Kossel & Kutscher (1900)	Osborne & Clapp (1906)	Osborne & Jones (1910)
Glycine		0.00		0.00	0.00
Alanine		0.50		2.23	8.98
Valine				0.29	
Leucine	17.25	11.25		18.60	17.95
Proline		1.49		6.53	9.01
Phenylalanine	6.96		4.87	6.23	
Aspartic acid	1.43	1.04		1.41	1.73
Glutamic acid	10.00	11.78		18.28	26.17
Serine				0.57	1.00
Tyrosine	3.20		10.06	3.55	3.55
Arginine			1.82	1.16	1.35
Histidine			0.81	0.43	0.82
Lysine			0.00	0.00	0.00
Tryptophan				0.00	0.00
Ammonia			2.56	3.61	3.64
				61.53	80.43

[1872-1935] initiated their famous joint studies on animal nutrition. In the meantime, Frederick Gowland Hopkins [1861-1947], the discoverer of tryptophan, had noticed Osborne's report that the seed protein zein lacked this amino acid. In 1906, Hopkins and Edith Gertrude Willcock [1879-1953] published a paper (21) showing that young mice fed zein as a sole source of protein did more poorly than comparable animals to whose diet tryptophan had been added.

A few words about Mendel and his relationship to Osborne. Mendel received his Ph.D. at Yale in 1893 for work with Russell Henry Chittenden [1856-1943], and ten years later he succeeded Chittenden as head of the Yale laboratory of physiological chemistry (22, 23). An outstanding teacher, Mendel made that laboratory the principal seedbed for the next generation of American biochemists. His collaboration with Osborne in the field of animal nutrition lasted nearly twenty years and produced more than one hundred joint papers, with special emphasis on the so-called indispensable amino acids and on vitamins. In this work, Osborne's highly purified protein preparations played a decisive role. Among Mendel's students at that time was William Cumming Rose [1887-1985], who later discovered threonine during the course

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of his sustained nutritional studies along the lines initiated by Osborne and Mendel (24).

Osborne collaborated to a lesser degree with other American scientists, for example Francis Gano Benedict [1870-1957] and Donald Dexter Van Slyke [1883-1971], but the most fruitful of these additional joint efforts was the one with noted pathologist Harry Gideon Wells [1875-1943]. Wells had worked in Fischer's laboratory with Abderhalden, and his interest in protein chemistry led him to examine the specificity of the anaphylactic response of sensitized guinea pigs to the injection of purified seed proteins supplied by Osborne. These experiments, reported in 1911, revealed further cases of the individuality of proteins previously thought to be identical (25).

To summarize briefly, the most important features of Osborne's research until about 1915 were successively the purification of seed proteins, the amino acid analysis of these proteins, and their use for studies of animal nutrition and immunological specificity. Afterward, Osborne and Mendel were led increasingly into such areas as the vitamin content of various foods and some medical aspects of nutrition.

I turn now to Osborne's research group. At any given time, it was quite small and composed almost entirely of Yale graduates (see Table 2). It seems that when one of his assistants was about to leave, Osborne would ask a professor in the Yale Chemistry Department (usually the organic chemist Treat B. Johnson) to recommend someone. Only one of these men - Hubert Vickery - may be said to have achieved scientific distinction. A Canadian who had come to Yale as an 1851 Exhibition Scholar, Vickery had begun graduate work with Johnson, who recommended him to Osborne. In 1928, "Vic" (as he was known to his friends) succeeded Osborne as head of the Biochemical Laboratory at the Experiment Station, and in the years that followed he instituted a fruitful program of research on the metabolism of leaves (26, 27). Except for Breese Jones, who continued to work productively on proteins after he left Osborne, none of the others listed in Table 2 appear to have made a significant mark in the scientific literature. I should note, however, that in 1913 Frederick Heyl became the first research director at Upjohn and during the 1930s he initiated that company's pioneering program on steroid hormones (28).

Osborne attracted few post-doctoral guests, but among them was Edwin Cohn later[1892-1953], who was in New Haven in 1917. At Harvard, Cohn led a research group which made many important contributions to the study of the physical chemistry of proteins (29). Only one post-doctoral associate came to the Osborne laboratory from abroad. He was Albert Charles Chibnall [1894-1988], who had received his Ph.D. in 1921 at Imperial College London for work on leaf proteins. When Chibnall arrived in New Haven, Osborne was still in Vermont for his summer vacation - the partridge season had not yet ended - so Chibnall made contact with Mendel, who impressed him greatly. Vickery later recalled that (30):

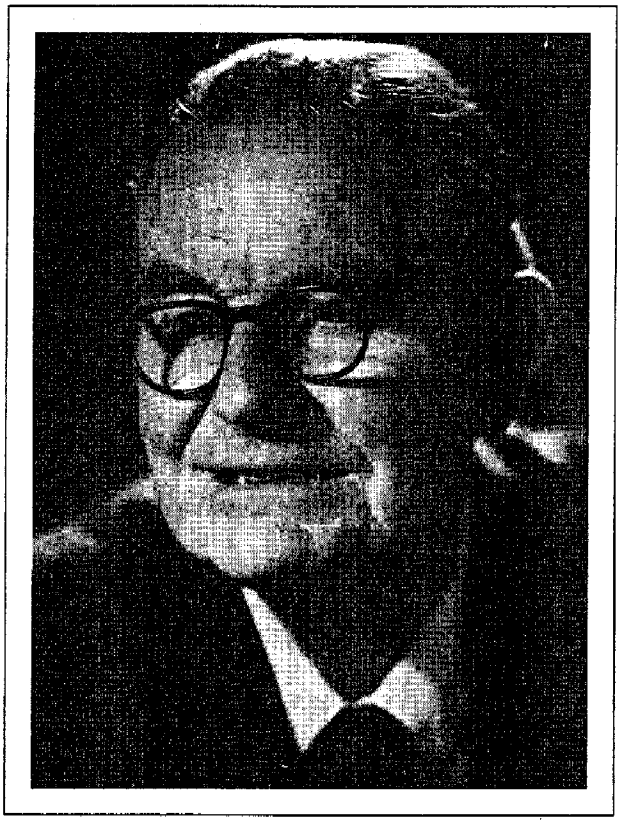
Table 2. Osborne's Research Assistants

1891-92	Voorhees, Clark Greenwood [1871-1933]	Yale Ph.B. 1891
1894-1900	Campbell, George Flavius [1870-1902]	Yale Ph.B. 1892
1901-07	Harris, Isaac Faust [1879-1953]	Yale Ph.D. 1915
1906	Gilbert, Ralph Davis [1878-1919]	Yale Ph.D. 1904
1906-08	Clapp, Samuel Hopkins [1876-1952]	Yale B.A.; Ph.D. 1908
1906-09	Brautlecht, Charles Andrew [1881-1964]	Yale Ph.B.; Ph.D. 1912
1908	Heyl, Frederick William [1885-1968]	Yale Ph.B.; Ph.D. 1908
1908-28	Leavenworth, Charles Stanley [1879-1948]	Yale Ph.B. 1902
1908-10	Jones, David Brees [1879-1954]	Yale Ph.D. 1910
1909-10	Liddle, Leonard Merritt [1885-1920]	Yale Ph.D. 1909
1910-11	Guest, Herbert Hartley [1884-1956]	Yale Ph.B.; Ph.D. 1912
1916-23	Wakeman, Alfred John [1865-1956]	Yale Ph.B. 1887
1920-28	Nolan, Owen L. [1888-1958]	
1921-28	Vickery, Hubert Bradford [1893-1978]	Yale Ph.D. 1922
1924-28	Nolan, Laurence S. [1890-1984]	

> When Osborne returned a few weeks later, I told him of this Englishman who wanted to join us. Osborne was very busy that morning, and my tale was greeted with a succession of grunts and finally, 'Well, is he any good?" Assured on this point, he finally said, "All right, bring him out." Chibnall succeeded in charming Osborne within the hour, and I was instructed to install him in the laboratory at once. As soon as Osborne saw his command of technique, his original approach, and his industry, he happily turned over all of the work on leaf proteins to him.

To this report should be added Chibnall's own later recollections (31):

> I had been warned by Mendel of [Osborne's] nervous temperament, and the possibility that he might be taciturn when we met, but he greeted me cordially and in a very short while I felt quite at ease. I think I touched a chord to which his nature readily responded, for in our first talk I mentioned my home background, and he recognized in me someone who had taken the same path as himself, embracing science in spite of family efforts to divert him to more practical pursuits. As I got to know him better I learned to appreciate the warmth of his interest in things that he cared for, and the scarcely less conspicuous indifference to matters which lay outside the well defined boundary lines of his sympathies.



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In a later memoir, Chibnall noted (32):

> I was surprised to find how narrow his interests were. Almost as soon as I came into touch with him I was to learn, to my surprise, that plant physiology made no appeal to him at all.

I have quoted these recollections about Chibnall's association with Osborne for several reasons. The most important is that they reveal something of Osborne's style of leadership in his latter years, especially in his ability to recognize scientific talent, as was also evident in his treatment of Vickery. They also confirm the impression that Osborne was a man of limited scientific outlook.

To these reasons I must add an obligation to pay tribute to Chibnall's role in the development of modern protein chemistry (33). In his later research on proteins, as professor at Imperial College from 1929 until 1943, and then as the successor of Hopkins at Cambridge until 1949, Chibnall followed the trail charted by Kossel, Fischer, and Osborne. By about 1940, however, with the advent of the chromatographic method introduced by Martin and Synge, Chibnall had begun to see the demise of that approach. At Cambridge, he suggested to a young post-doctoral student named Frederick Sanger that fluorodintrobenzene might be a good reagent for the determination of the amino-terminal groups of proteins, and that insulin (whose amino acid composition Chibnall's group had determined) might be a good protein to start with.

The rest is well-known history. The analytical chemistry of proteins, begun during the 1830s by Gerrit Mulder and Justus von Liebig, was completed during the 1950s by Sanger and by Stanford Moore and William Stein. In this transmission of a chemical heritage, the role of Thomas Burr Osborne deserves to be remembered.

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