CLXIX. THE CENTENARY OF WÖHLER'S SYNTHESIS OF UREA (1828—1928).

By FREDERICK GOWLAND HOPKINS.

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CHARACTERISTIC of modern intellectual progress is the growth of the historic sense. Hence the popularity of commemorative celebrations, recalling not alone the outstanding events of political and social progress, but also those events which are landmarks in intellectual advance. This is surely a commendable form of piety, promoting in current thought a sense of continuity and a proper perspective.

In the history of Biochemistry the synthesis of Urea by Wöhler is certainly an outstanding event. Few who are concerned either with chemistry or biology can be unaware of the date of its accomplishment, for there is scarce a textbook that does not mention that date with insistence. A reminder therefore that the present year marks its centenary would be wholly superfluous. It has been felt however that in the records of the Biochemical Society there should be some indication that due notice was taken of the arrival of that centenary, and as a very inadequate method of marking such recognition I have been given the privilege on the present occasion of saying a few words about Wöhler's famous synthesis.

Now we should I think realise at the outset that in our commemorative piety we may be apt to overestimate the effect of this or that discovery upon the thought of its own period. In our backward perspective we see it stand out in all its importance, but it does not follow that this importance was immediately felt. I think, indeed, that our textbook writers in their familiar references to the event which we now have specially in mind have tended to exaggerate its effect upon the thought of its time.

The intrinsic historic importance of Wöhler's synthesis can hardly of course be exaggerated. So long as the belief held ground that substances formed in the plant or animal could never be made in the laboratory, there could be no encouragement for those who instinctively hoped that chemistry might join hands with biology. The very outermost defences of Vitalism seemed unassailable. We now recognise that Wöhler's discovery effectively breached these outworks, making it necessary for Vitalism to retreat behind inner and more subtle defences. The breach in question had to be widened, however, by later efforts, before very many recognised all its significance.

¹ Here slightly amplified.

Before proceeding, I ought perhaps to refer, parenthetically at least, to the work of the English chemist, Hennell, because his synthesis of ethyl alcohol has sometimes been put forward as being, rather than Wöhler's, the actual pioneer organic synthesis. The significant part of Hennell's work—his demonstration, namely, that the sulphovinic acid which (following Faraday) he had prepared from olefiant gas yielded alcohol on distillation—was as a matter of fact published by the Royal Society¹ in the same year as that in which Wöhler's paper appeared. We may well therefore hold the accomplishment of both syntheses in pious memory to-day. But with respect to their significance, it should I think be admitted that since the vital nature of alcoholic fermentation was not recognised in the day of Hennell and Wöhler, the artificial production of a substance actually arising in the living animal body should have had for contemporary thought the greater significance.

It is well, however, for the sake of historical accuracy, to realise that as I have already indicated this significance was not fully recognised when the work was first published. I may remind you that Wöhler himself in communicating his discovery² makes no resounding claims. He remarks merely, in the beginning of his paper, that the research he is to describe "gave the unexpected result that by the combination of cyanic acid with ammonia urea is formed; a fact (he continues) that is so far noteworthy in that it furnishes an example of the artificial production of an organic, indeed a so-called animal substance, from inorganic materials." The rest of this classical paper is wholly descriptive until, at its close, the author shows in a sentence that he is alert to the significance of the isomeric change which is involved in the synthesis. The adjective "noteworthy" (merkwürdig) is all that he allows himself in comment on his successful passage from the inorganic to the organic.

It is however not surprising that Wöhler when announcing his discovery wrote with this restraint, for it would seem that he himself was really doubtful whether he had, after all, built a bridge across a gulf. In a letter to Berzelius dated from Berlin, Feb. 22nd, 1828³, he writes as follows to his former chief: "You will perhaps remember that during a research carried out in those happy days when I still worked with you, I found that whenever one endeavoured to combine cyanic acid with ammonia, a crystalline substance appeared which was neutral, and gave the reactions neither of cyanic acid nor ammonia." This passage refers to work done in 1825. The letter I am quoting informs Berzelius, "for the first time," that the neutral substance in question was urea. "I must now tell you," writes Wöhler, "that I can make urea without calling on my kidneys, and indeed without the aid of any animal, be it man or dog." But at the end of a somewhat long letter he puts this question to his correspondent: "This artificial production of urea—can one take it as an example of the formation of an organic substance out of inorganic materials?

¹ *Phil. Trans.* 1828, p. 365.

² *Poggendorff's Annal.* Bd. 12, 243 (1828).

³ *Briefwechsel, Berzelius und Wöhler*, edited by O. Wallach, Bd. 1, 206 (1901).

It is striking that for the production of cyanic acid (and, no less, of ammonia) one must always start with an organic substance. The Natural Philosopher might well say that from animal carbon and from the cyanic compounds made from it the Organic has by no means disappeared, and it is for this reason that it may be always possible to reproduce an organic substance from these materials." An attitude sufficiently critical!

I cannot refrain from quoting the somewhat famous reply of Berzelius to this communication¹, because it rather strikingly bears on my present theme—the effect of Wöhler's discovery upon contemporary minds. Berzelius wrote a letter which starts with sheer raillery of a Rabelaisian kind. In quoting it I propose to retain the language of a German translator! "Nachdem," says Wöhler's mentor, "Nachdem man seine Unsterblichkeit beim Urin angefangen hat, ist wohl aller Grund vorhanden, die Himmelfahrt in demselben Gegenstand zu vollenden—und wahrlich, Hr. Doktor hat wirklich die Kunst erfunden, den Richtweg zu einem unsterblichen Namen zu gehen.... Sollte es nun gelingen noch etwas weiter in Produktionsvermögen zu kommen (vesiculae seminales liegen ja weiter nach vorn als die Urinblase), welche herrliche Kunst in Laboratorium der Gewerbeschule ein noch so kleines Kind zu machen—Wer weiss? Es dürfte leicht genug gehen." Such was the first reaction of the great Swede's mind to Wöhler's announcement. Persiflage! Berzelius does not even trouble to answer the direct question posed for him. In the same letter he does, it is true, finally congratulate his former assistant upon a "right important and beautiful discovery," but it is noteworthy that his interest in it centred on the isomeric change involved in the synthesis. "It is an altogether striking circumstance," he remarks, "that the character of a salt is so completely absent (from the product) when the acid unites with ammonia, a circumstance which will certainly be very enlightening for future theories." It is clear indeed that Wöhler himself was on the whole more intrigued with this side of his discovery than with its bearings upon the vitalistic position. The method of urea formation suggested to his mind that alkaloids might somehow arise on similar lines from the union of organic acids with ammonia, and he made attempts to test this view, in the case of cinchonine for instance, by submitting the substance to electrolytic decomposition.

We should next, I think, take note of the attitude of Justus Liebig, who was in the closest touch with Wöhler and whose influence upon the thought of the time was great. Considering how much Liebig's own work contributed to the growth of clear thought and objective views in the domain of plant and animal chemistry, it is puzzling that he himself should so long have clung to his conception of a Vital Force. He does not, it is true, seem to have thought about it as a "Force" necessarily outside the category of known "forces." Living to-day he would probably have spoken of it as an unknown form of energy. It was for him an agency which reacted with (and in general opposed!) the forces of chemical affinity as understood by him. Even so late as 1842 he

¹ *Briefwechsel, Berzelius und Wöhler*, edited by O. Wallach, Bd. 1, 208 (1901).

wrote: "The vital force appears as a moving force or cause of motion when it overcomes the chemical forces (cohesion and affinity) which act between the constituents of food, and when it changes the position or place in which their elements occur; it is manifested as a cause of motion in overcoming the chemical attraction of the constituents of food and is further the cause which compels them to combine in a new arrangement, and to assume new forms¹."

This was written fourteen years after the synthesis of urea, with which of course Liebig was from the first intimately familiar. That accomplishment clearly did not convince him that the forces which "compelled" the elements to "combine in a new arrangement" in Wöhler's laboratory could do the same in the living body. It is but fair to remember that some years later Liebig was coming to the conclusion that it was after all unjustifiable to assume the existence of a special vital force until more was learnt concerning the scope of known physical forces. To anyone who reads the 20th letter in the 5th edition (1851) of his *Chemische Briefe* this change of mind will be evident. By this time however Wöhler's synthesis had become an old story.

Great as is the debt of Biochemistry to Liebig, there can be no doubt that he lacked physiological knowledge and his *ex cathedra* utterances sometimes tended to obscure the facts. Berzelius insisted on this and spoke of current theories based solely upon chemical speculations, untested on plant or animal, as "Probabilitätsphysiologie"!

I must not here leave you with the impression that Liebig's obsession was shared by all the leading minds of that day. Dumas, for instance, though later a supporter of many of Liebig's much disputed views about other aspects of biochemical phenomena, early dissociated himself from a belief in any Vital Force. It may be noted that in 1833 Dumas met Wöhler for the first time. This was in Paris and the two evidently saw a good deal of each other there, for Wöhler sent to Berzelius² an extremely acute appraisal of the character and qualifications of the French chemist. Three years later, in 1836³, Dumas allowed himself the following very definite statement of faith—"In my belief there are no substances which, in any peculiar sense, are to be called organic. I visualise in organised beings only very slowly working forms of apparatus which act upon materials at the moment of their genesis and thus produce from a few elements very various 'inorganic' compounds." (The quotation marks to the word 'inorganic' are mine.) This statement has a very modern ring; I am even inclined to think that it contains a hint for ourselves. It is impossible to say how far the synthesis of urea had affected the thought of Dumas; he was certainly familiar with it.

In seeking evidence concerning the contemporary effect of Wöhler's work we may perhaps do well to turn from the minds of the Olympians and ask how it affected lesser men; the men who in the main were concerned with teaching

¹ *Animal Chemistry*, edited by Wm Gregory from the author's ms., 2nd ed. 1843, p. 204.

² *Briefwechsel*, Bd. 1, 535.

³ *J. prakt. Chem.* 7, 298 (1836).

and the writing of students' textbooks. They were little concerned with philosophical niceties, but any considerable change in the intellectual atmosphere must have affected their writings.

The chemical textbooks published during the decade which followed Wöhler's publication, while duly chronicling the success of the synthesis and its nature, seem to make little of its anti-vitalistic significance, even in the case of those specially concerned with what we should now call biochemistry. A representative book of the kind was the *Medical Chemistry* of Carl Fromherz, of which the first volume appeared in 1832 and the second in 1836. Fromherz was professor of Chemistry at Freiburg and an able writer. His book was one of the best of its time and I think it is worth while to note the attitude of this author to the event which is occupying our attention. Fromherz, in a section of his book devoted especially to urea, describes Wöhler's synthesis in detail, remarking with restraint that it is an accomplishment of much interest. But in the theoretical discussion contained in the book, when dealing with what he believed to be the fundamental distinction between inorganic and organic chemistry, he frankly resigns himself to a belief in a vital force, and shows no signs of feeling that Wöhler's work ought to affect that belief in the least. There were at this time several other writers who though far from being obscurantists, continued to believe in a Vital Force; though among them were some who, like Fromherz, had the sincerest belief in the importance of chemical studies to biology. The men I mean thought on chemical lines and it was for chemical reasons (as they would themselves have claimed) and not because of philosophical preconceptions that for some years after Wöhler's synthesis they relied upon something unique as the causal factor in biochemical phenomena.

Their attitude was due in fact to the dominance in contemporary thought of that rigid dualistic theory of chemical affinity which we associate especially with the name of Berzelius.

Inorganic compounds arise, it was held, only when elements of opposite electric charges—or groups dominated by elements with opposite electric charges—come together. Now the writers I am quoting found it difficult to see how in the building up of the complex carbon compounds, produced by the plant or animal, this rigid duality could possibly play an effective part, and their doubts expressed more wisdom perhaps than Berzelius himself showed in his struggles to apply his views in organic chemistry.

I am dealing with the matter far too briefly to make clear the weight of such considerations as judged from the standpoint of the time; but to Fromherz and many of his contemporaries it was plain that, while inorganic compounds arose under the influence of affinity, as then understood, another, and quite different, force must control the knitting together of complex organic compounds. For these plain chemical thinkers the Vital Force was just this unknown controlling agency. They had no other commitments with regard to it and were much less dogmatic than was Liebig in his earlier days.

You will see that Wöhler's synthesis was not one to disturb very greatly such views as those of Fromherz. The union of ammonia and cyanic acid is a straightforward dualistic happening, and the isomeric change involved—though Wöhler himself was alert to its general significance—was still merely obscure to the majority.

In parenthesis, I may say here that I cannot find that the first artificial synthesis of an organic substance formed a text for discussion in any of the Journals of Wöhler's time devoted to philosophical or general intellectual interests; though a complete research into this matter has been beyond my leisure. One gets the impression that the intelligent lay public which took cognizance of scientific progress in those days was hardly aware that anything worthy of its attention had yet arisen from the application of chemistry to the plant or animal.

Returning to the textbook writers of the time, one feels that it was a sound instinct in these pioneers to emphasise in their own way that there is all the difference between the methods of the living body and the classical methods of the laboratory. That the agencies which control biochemical events work on lines of their own is the basic circumstance which alone justifies the claim of biochemistry to rank as a self-standing scientific discipline. It is those special agencies and their impact upon molecular structures which constitute the peculiar field of biochemical study, and should be its final concern. The information which artificial syntheses afford in proof of constitution is of course absolutely essential to the progress of biochemistry, but for the genuine biochemist its attainment is a means to an end and not an end in itself. We can never be content with what Berzelius would have called "Probabilitätsbiochemie."

Fortunately we are no longer compelled to visualise an ultra-physical Force as the determinant of chemical changes in the living cell. Just now Surface Catalysis as an agency justifiably dominates our field of view, though it may be doubted whether it alone will give us the complete picture we hope ultimately to see. It is, I think, for the progress of biochemistry of good augury that the organic chemist now views molecular structure as a dynamic and not a static affair, for it is sure that molecules, while playing their diverse parts in the intense turmoil of life, may be never more than momentarily in that stable condition which they have assumed when they get into bottles on our shelves.

It is certainly instructive and not necessarily humiliating to realise that the molecular structure of a substance already synthesised one hundred years ago, a substance with a molecular weight of no more than 60, is yet a matter for debate. It is not surprising. A molecule of such biochemical prominence is likely to assume during its complex metabolic career just as many forms as with due regard to the decencies of valency it can manage to assume! I think we should be grateful to Prof. Werner for the "ring" and "open" structural formulae of urea, even if their reality be not yet proven. I also

think, however, that carbamide may not be absent from the laboratory of living tissues. After all, ammonia *does* meet with carbon dioxide there, and the liver *can* dehydrolise ammonium carbonate. Anyhow, it is significant that a century after Wöhler's synthesis we are still discussing this matter, and are realising in consequence that we must revise our too dogmatic views as to precisely how urea arises from amino-acids in the body.

It would indeed not be out of place when celebrating the centenary of its synthesis to recall how interesting are the problems which, in all its relations, this familiar substance still presents. I must not of course stop to survey them.

Nevertheless, just to widen a little the scope of my remarks, I will venture in concluding them to put before you certain considerations of a more biological sort which seem to me to possess no small interest. On surveying the field of comparative biochemistry we remember that urea, with all its obvious merits as an excretive, is in the case of certain animal groups replaced by insoluble uric acid. The replacement at first sight seems a casual happening and has puzzled many. My colleague, Dr Joseph Needham, has been considering this problem and has come to a conclusion which with his permission I will submit to your judgment. The evidence on which it is based will be found in an article which Needham is publishing in *Science Progress*, and later, in a chapter of his forthcoming book on the Chemistry of Development.

The thesis is that the conditions of its embryonic existence determine whether an animal shall excrete urea or uric acid. If its embryonic development occurs in an egg subject to aquatic conditions which allow the end-products of metabolism to diffuse freely away, or if, as in the case of the viviparous mammal, the maternal circulation secures the same efficient removal, then the embryo, and, by established metabolic habit, also the adult, excretes urea. If on the other hand the embryonic life is passed in a closed box, such as is the bird's egg, then the embryo, for good reasons, as we are to see, turns to uric acid as an end-product and excretive, and the adult continues the tradition.

Consider the state of affairs in the hen's egg. Up to the eleventh day water accumulates in the allantois in sufficient amount to transport the uric acid produced up to that date. Then water is re-absorbed from the allantoic cavity leaving uric acid behind. Later water is again excreted, carrying more uric acid. "It is," to use Needham's words, "as if the water acted as an endless belt-conveyor transferring uric acid from the cells of the embryo into the allantoic liquid and then returning to convey more." Thus the embryo itself escapes any accumulation of its excretion. On the other hand it is hard to see how embryonic development in the closed system of the bird's egg could proceed satisfactorily if the end-product of its metabolism were a very soluble and highly diffusible substance like urea. It would accumulate in equal concentrations throughout the contents of the egg, and the embryo itself would, as Needham remarks, become more and more uraemic! Under these conditions the less soluble excretion possesses all the advantages. Needham

has brought together all the available data concerning the excretion of urea and uric acid respectively in the various animal phyla, and the weight of the evidence strongly supports the view that embryonic conditions determine the nature of the end-product. That the adult continues to behave on the same lines as the embryo merely illustrates once more the fact that every organism is a product of its past. Such considerations are doubtless of the teleological kind, but they help us to understand an evolutionary puzzle.

Perhaps I have said too little about Wöhler's synthesis and too much about other matters, and what I have said must seem to have minimised rather than emphasised the importance of its influence upon thought. Yet its intrinsic significance is of the greatest. Not, it is true, until the structure of biochemical science had grown greater than it was in the days of Wöhler and his immediate contemporaries was it recognised as one of the foundation stones of that structure; but as such we now see it.