HANS KREBS: NINETEEN NINETEEN AND AFTER

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At the time I am writing these lines it is just sixty years since I first met Hans Krebs. So it is appropriate that I should appear in the ranks of those who wish to pay him a tribute on the occasion of his eightieth birthday.

Like his juniors in years, so his contemporaries are indebted to him; he has been a teacher of more than one generation of biochemists. The extent of my own debt will become clear as my tale unfolds.

We met as undergraduates at the University of Freiburg-im-Breisgau in the autumn of 1919. This was shortly after the end of the first World War. Things were very difficult at the German universities. The end of the war brought the ex-combatants back, anxious to finish their interrupted or postponed studies. These veterans crowded the lecture rooms, together with the school leavers. There was a scarcity of almost everything. Our digs were cold, as there was little fuel. The university authorities kept some of the lecture theatres open for us in the evenings, so that we could have a reasonably warm place to sit in. Food and many other necessities of life were scarce likewise.

Still, I cannot remember that we were ever downhearted. On the contrary, that period at Freiburg stands out in my memory as a happy and golden time. One spent all one's leisure hours, summer and winter, in the glorious surroundings of Freiburg, and during our working hours we thoroughly enjoyed our course. We were very fortunate: we had a number of interesting teachers. Freiburg was one of the few German universities where biochemistry was an obligatory part of the practical course in physiology. Our professor was Franz Knoop; he also gave biochemistry lectures, where I first heard about things like β-oxidation of fatty acids.

It was actually during that first winter semester in 1919 that Hans was amongst my teachers: he had volunteered to act as a student-demonstrator in the embryology course, given by Wilhelm von Möllendorf. I learnt much in that course.

Thus, my earliest memories of Hans are closely linked with what I remember of terms like blastula and gastrula. He was one of a group of students who demonstrated the slides that they had presumably looked at a little while before. These were excellent slides, and I remember still making use of them about twenty years later when I had to demonstrate in the Histology Class at Cambridge, from 1934 to 1944.

Incidentally, von Möllendorf, a very competent anatomist and histologist, was Rektor of Freiburg University when Hans was given the right to lecture at the University. Soon afterwards, (in 1933), when Hans had to leave Freiburg for good, he too lost his position. Fortunately he soon found asylum in Switzerland, I believe at Zürich, where he was offered the Chair of Anatomy.

I cannot exactly remember how long Hans remained at Freiburg, but in an old List of Members of the University from the Summer Semester of 1921 that has survived by some unexplainable freak, I find his name still listed, as stud.med., living at Wölfflinstrasse 14.

In our days it was the habit of German students to move from one university to another. We all made use of that privilege. I met Hans again at the end of our medical studies in Berlin, my own native city. I remember that he spent some time there in 1924 as an interne in the Third Medical University Clinic, directed by Alfred Goldscheider. It must have been at that time that he came to the notice of Bruno Mendel, a physician who worked at the Clinic. It was Mendel who recommended Hans to his friend Otto Warburg.

I had finished my medical studies a little earlier and had started research with Otto Meyerhof in Berlin-Dahlem in January 1925. In the following year, one day when emerging from the U-Bahn at the Station Thielplatz in Dahlem, I ran into Hans. He told

me that he had come for an interview with Otto Warburg, whose laboratory was in the same building as Meyerhof's. As we were walking towards the Institute together, I told Hans I had heard that Otto W. had the reputation of being a somewhat difficult person. Hans remained serene and unimpressed. At any rate, he got his job with Warburg, and I feel sure he did not come to regret it.

The Dahlem of the nineteen twenties has in recent years repeatedly been described by those who had the good fortune of living through that experience [1,2]. The men who introduced us into research have made scientific history. In addition, there were all the bright and keen contemporaries, a cheerful and stimulating company. All the time I was in Dahlem, Warburg and Meyerhof had their laboratories under the same roof; thus we had daily contacts. And since we all worked in closely related fields there was a community of interests; we often met during the lunch break. After a lapse of over fifty years, that period in Dahlem still appears like a golden age to me, like the Freiburg time, and as at Freiburg, both Hans and I made friends that have remained companions through a lifetime. Let us hope that Hans will find time to describe the impact that his period with Otto Warburg made in his scientific development. I have recently recounted how my first piece of independent work in Cambridge was related to what I had learnt in Dahlem in 1925 [3].

In 1930 I re-joined Meyerhof at Heidelberg, after a year at University College London, with A. V. Hill. By that time Hans had also left Dahlem and after a year or so at Hamburg-Altona had moved to the Medical Clinic at Freiburg. For him the period of apprenticeship was now over, and from now on the problems he was working on were of his own choosing. Freiburg and Heidelberg were near enough for us to meet for weekend visits. In my memory, one sunny summer Sunday stands out when David Nachmansohn and I came to Baden-Baden, to meet Hans who had travelled up from Freiburg. We spent that afternoon, lying in the grass, sunning ourselves and occasionally talking 'shop'. That might have been in 1931. In the summer of 1932 we went to the 14th International Physiological Congress in Rome. Scientifically it was a rewarding experience. I particularly remember a session on muscle biochemistry where Einar Lundsgaard showed that the breakdown of phosphocreatine could be made to lag behind muscle contraction provided the experiment was carried out at low temperature. It was an important observation that cleared the way for ATP to be recognised as the immediate energy donor in the contraction process.

After the Congress we spent a seaside holiday together at Forte dei Marmi, surrounded by physiologists and biochemists; I remember H. H. Weber and F. Knoop. We spent our time there with Alex and Alice von Muralt, and eventually they gave us a lift in their car, at least as far as Milan.

A few weeks later, probably in September 1932, I spent a weekend with Hans at Freiburg. This occasion I remember well. On the Sunday afternoon we were joined by our friend Paul Rothschild, then in the Medical Clinic at Frankfurt, with his friends, George and Carola Pickering. They had come from a holiday in the Black Forest, and they gave me a lift home to Heidelberg on their way to Frankfurt. The reason why this trip has so strongly impressed itself upon my mind is because we became aware, maybe for the first time, of the threatening Nazi menace. Previously all displays of party banners had been forbidden in the Land of Baden, but this ban had just been lifted. A gloom was cast over our spirits as we were driving home through a beautiful landscape in glorious evening sunshine, through all those lovely old towns and villages, all almost hidden under a deluge of brand-new swastika flags.

A few months later, by the time Hitler took over, I was back in Freiburg, this time as a patient in the Medical Clinic, with Hans as one of my physicians. I was in a pretty poor condition when I arrived there in December 1932, but as I was improving and allowed to get up, I spent more and more of my day in Hans' laboratory on the ground floor. Nowadays, when I go to call on the Metabolic Research Laboratory here in the Radcliffe Infirmary, I am reminded of that lab. at Freiburg. Now as then the lab. is not too far from the wards; already then it was a hive of cheerful activity and rather overcrowded. The place had great attractions for people who spent part of their time on the wards, but there were also some visitors from abroad. By the time I was there, Hans' papers on the biosynthesis of urea had been published and the work on the oxidative deamination of amino acids must have been virtually completed. Thus, by that time Hans had already established himself as one of the outstanding scientists of our generation. Moreover, he had had the opportunity of demonstrating his great qualities as a teacher of researchers. He had also proved his abilities as a physician; in my case he had

shown that a bladder stone that troubled me was an oxalate stone!

Thus it came to pass that at the time of the Hitler takeover we were living under one roof. It was a difficult time for the Clinic. The Professor of Medicine, J. S. Thannhauser, an able biochemist, was a Jew, and the campaign against him and his colleagues began early on. Actually, when the end came for them all, I had recovered sufficiently and left the Clinic and Germany at the same time: that was on April 1st, 1933, the day on which the Nazis declared a boycott of the Jews. I travelled only a very short distance, from Freiburg to Basel, a train journey of about an hour but that was my last stay on German soil until 1950. I had already had an offer of hospitality from A. V. Hill, to come back to University College, London, where I had been in 1929–30: I went there towards the end of May 1933.

Two letters from Hans have survived, addressed to me while I was still in Switzerland. The first came from St. Peter, a resort in the Black Forest. It is dated Easter Monday 1933; Whitaker's Almanack tells that was the 17th of April. In it he tells me that on the preceding Tuesday all Jews were 'given leave of absence until further notice' (actually, Hans was allowed to keep his private apartment in the Clinic a little longer). He was busy with literary work, but was also enjoying the marvellous spring sunshine; he wrote that for the first time since our stay in Forte dei Marmi he can expose his bathing suit to the sun. 'I really am lucky with the weather'.

As to the literary work, I find that the big paper on amino acid metabolism [4] was received at the editorial office of *Hoppe-Seyler's Zeitschrift* on 18th April; that means that this manuscript was completed before he went to St. Peter. There is a second, shorter, paper, also on amino acid metabolism [5], received by the editors on 23rd May; that might have been the paper that he was busy with in St. Peter.

In this letter, and in a subsequent one from Freiburg, dated 4th May, he talks of his determination to leave Germany soon. A possible move to Switzerland was not pursued for long; in the second letter he says he is determined to come to England as soon as possible, and he mentions an invitation from Hopkins to come to Cambridge.

When Hans left Germany, he had several achievements to his credit. He had been physician in charge of one of the wards in the University Medical Clinic, and he had recently been granted the 'Venia legendi', i.e., the privilege to lecture in the University. He had published several substantial papers. The first, that with Henseleit [6], was on the formation of urea in the animal body. Its publication immediately established his reputation. It gave the answer to an important unsolved problem, that of the site and of the mechanism of urea biosynthesis in the mammalian body. It also demonstrated a physiological role for arginase, an enzyme that had been known for some time. The most important features of the work were the discovery of the catalytic role of ornithine and the proposal of the 'urea cycle'. This was the first metabolic cycle to be formulated, an idea that has played a prominent part in his later work. These reaction sequences have one characteristic feature: the metabolic events were kept going by feeding in one of the metabolites; of the end products of the sequence, one was returned into the metabolic pool while another appeared as the end product. The general implications of this idea were at once grasped by biochemists. The paper also contains the description of the 'Krebs–Ringer' solutions; these are still widely used by many people who may never have read the original publication.

The two papers on amino acid metabolism also broke new ground. Oxidative deamination had been postulated to occur for a long time; here was a clear-cut demonstration of the quantitative relationship between oxygen consumed and ammonia formed. The full elucidation of amino acid breakdown had to wait for another few years, until the discovery of transaminases by Braunstein. A more immediate gain was the purification of D-amino acid oxidase and the discovery of flavin-adenine dinucleotide by Warburg and Christian [7].

Hans arrived in England soon afterwards, at 7.45 a.m. on 20th June 1933. I met him at Victoria Station and he spent a couple of nights with me, in my aunt's house in London. I seem to remember that he had to choose between Oxford and Cambridge. Hans saw the two places and quickly accepted the invitation from Hopkins, where there was the possibility of a University position in the not too distant future. He immediately moved to Cambridge.

He could not have made a better choice. At that time, Cambridge was taking the place that Dahlem had held in the 1920s. Hopkins was the Grand Old Man of Biochemistry, and in the 'Tea Clubs' (research seminars) in his department all the Cambridge biochemists, and many visitors, took part. There were

many reasons why Hans should find the place congenial for his line of research and why people were prepared to profit from his arrival. I do not think that Hans was ever looked upon as a representative of the Warburg school. The attacks of Otto Warburg on David Keilin and Malcolm Dixon were by no means forgotten (those on the work [8] of Flora Jane Ogston and David Ezra Green were still to come!). However, some personal relations had been established at the Heidelberg 'Iron' Symposium, and altogether the old arguments as to 'oxygen activation' and 'hydrogen activation' were beginning to lose their significance as a more unified picture of tissue respiration was emerging. At any rate, Hans was not identified with these arguments. As to methods, Cambridge was a place that had played a leading part in the introduction of manometry although, on the whole, the differential 'Haldane–Barcroft' models were in favour. But, since Hans had managed to bring two whole Warburg baths plus 24 manometers with him from Freiburg, his example counteracted this tendency.

Hans was soon established in the Sir William Dunn School. He occupied part of one of the large laboratories on the first floor, which he shared with Norman Pirie. Once, while I was still in London, I came over to do a few experiments in that lab. with some equipment that I did not have at University College. The lab. space was less than in Freiburg, but things ran on essentially similar lines as at Freiburg, except that there was also one additional blackboard, on which Hans wrote down all new words, to be added to the vocabulary that he had already acquired. A number of people were already working with him.

In the summer of 1934 I also moved to Cambridge, to the Physiological Laboratory. For the first few weeks we lived on the same premises, but for his last Cambridge year Hans moved out, I think to Little Shelford. I have every reason to be grateful for this move, because soon he introduced me to one of his neighbours out there, Derek Richter, with whom my friend Hans Schlossmann and I started a very fruitful co-operation. That was in 1935, the year Hans left Cambridge for Sheffield. There he built up the laboratory of which his present laboratory is the offspring.

Others are better qualified than I am to reminisce about Hans' activities at Sheffield. I cherish recollections of weekend visits before the War, when we explored the Peak District. And during the War, I once stayed with Hans and Margaret, presumably when I came up for a meeting. After the War, the MRC Unit began its formal existence, and it flourished until 1967, when Hans retired from the Oxford Chair. I first visited it in 1947, when my wife and I returned from the first Edinburgh Festival and spent a weekend in Sheffield. And in the early 1950s my friend Arnold Welch and I attended the symposium on CO_2 fixation at Sheffield. That was just a few years before the move from Sheffield to Oxford when the famous Scala Cinema, in which some of the laboratories were housed, was replaced by the MRC 'Hut' and later by a floor of the building that now contributes to the Oxford skyline.

I have been asked: when was it that one first became aware of Hans' exceptional abilities? I hope that what I have told here has indicated what my experience has been. When he was an undergraduate he had impressed his teachers, for example, von Möllendorf. By the time he returned to Freiburg there cannot have been much doubt about his abilities.

What I have told also accounts for his great attractiveness for younger scientists. For those eager to work there was no better place to go to. He always created an air of cheerful activity around him. That has remained unaltered over the years and makes a visit to the laboratory at the Radcliffe Infirmary a pleasure.

Some time ago I listened to a talk by the great Swiss conductor Ernest Ansermet. He was, I think, talking about Stravinsky. He said the characteristic of a great artist was a quality that he called authenticity. I was immediately reminded of Hans Krebs. I do not find it difficult to recognise this quality in a scientist and I see it in his work.

Historically, I see him as standing in the line of the great 'physiological chemists'. This line includes names that we were very familiar with when we were young. There we find the names of physiologists like Claude Bernard and of clinicians like Oskar Minkowski. It was this tradition that Hans had already imbibed in his years as a pre-clinical and clinical student, before he went to Otto Warburg in Dahlem. There he was exposed to a new stream of thought. Warburg was a student of Emil Fischer, the great organic chemist, and of Warburg's own discoveries those that are most closely related to chemistry are those that we best remember today. We should also remember him as a brilliant technical innovator.

What Hans carried away from Dahlem was the scientific outlook and discipline and also much of the new methodology that Warburg had introduced. In

his own work, tissue slice technique and manometry were prominent from the very beginning and the development of these two useful methods attracted the many younger colleagues who joined Hans, from his Freiburg period onwards.

Authenticity I also see in his formulation of the tricarboxylic acid cycle, a sequence of metabolic events that has ramifications of almost ubiquitous relevance to all metabolism. The isolation and purification of the enzymes involved Hans left to others. This is in keeping with his own interests. He was content to follow the metabolic aspects; the molecular events were studied by others. I see an analogy here to Warburg's exploitation of the work on D-amino acid oxidase already mentioned. Altogether, the development and upsurge of the field of molecular biology did not deflect Hans from his own course. What I find satisfying is that the recent developments in biochemistry brought the two streams of study, that of the metabolic pathways and that of the molecular changes, closer together. Hans and his colleagues in recent years have been chiefly interested in regulation of metabolism. Regulation has also become a major interest of the molecular biologists, those primarily interested in the conformation of macromolecules and the way that conformation is modified by metabolites.

In more ways than one, development has turned full circle. Almost half a century ago I watched Hans build up his first independent laboratory. That was in a University Department of Medicine, where he and some of his colleagues also had clinical responsibilities. Today, once again, we find him and his coworkers installed in a Department of Medicine and engaged in work that has immediate relevance to the clinicians' interests. I am sure that is an environment entirely to his taste. May he long enjoy it, and may he long serve as a teacher and guide.

References

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