

## Seventy Years Ago January 31st 1933 and the clarification of urea biosynthesis

Giorgio Semenza<sup>a,b,\*</sup>

<sup>a</sup>Swiss Federal Institute of Technology, ETH-Zentrum, POB 35, CH-8092 Zurich, Switzerland

<sup>b</sup>Dipart. Chim., Biochimica e Tecnol. per la Medicina, Univ. of Milan, Via Saldini 50, I-20133 Milan, Italy

For anybody browsing through a textbook of biochemistry in 2003 it is ‘obvious’ that urea is synthesized via the ornithine cycle. But in the twenties this was far from obvious. At that time it was known that urea was the major end product of nitrogen metabolism in mammals and adult amphibia, but virtually nothing was known of the biochemical processes which led to it. Clementi, a young physiologist from Sicily, mainly working in Germany, had found that arginase activity was present *solely* in *all* livers of uritelic species (*‘la legge dell’arginasi’*). This strongly suggested that (i) arginase was involved in urea synthesis (most likely as its immediate precursor) and that (ii) the liver was the organ where much or all of urea biosynthesis took place. Yet, in the labs all attempts to obtain urea synthesis in homogenized or even just minced liver tissue constantly failed.

In the late twenties/early thirties Hans Krebs was a young M.D. working with Warburg. He learned from Warburg that most problems of ‘physiological chemistry’ are, in fact, chemical and/or physical problems and could (or should) thus be tackled as such. He also became acquainted with up-to-date techniques – some elaborate (e.g. the ‘Warburg apparatus’), and some fairly simple ones, e.g. how to prepare *thin* slices of fresh liver tissue. These liver slices (in which the diffusion of, say, oxygen or substrates was not limited by the diffusion through a thick tissue layer) showed ‘intact’ metabolic activity – e.g. respiration and glycolysis.

At the end of the stay in Dahlem, Warburg, who had recognized Krebs’ gifts, nevertheless judged his knowledge in chemistry inadequate for a biochemist and thus advised him to return to medicine. But Krebs followed this suggestion only in part: he accepted the offer from Prof. S. Thannhauser, the head of Medicine in Freiburg in Breisgau, who set up a lab for him in the basement. Krebs, who spent all day within the Clinic, could thus fulfill his medical duties in the ward, while at the same time working in the lab and supervising his few associates (particularly K. Henseleit).

Krebs’ work with the liver slice technique turned out to be very successful and notable in at least two respects: a first novum was the investigation of a *synthetic*, rather than a *degradation* biochemical process: upon addition of some amino acids, most notably ornithine, liver slices produced far *more urea* than that which could have derived solely from the nitrogen of the amino acid added. By critically ordering the formula of the amino acids that stimulated urea production, Krebs and Henseleit identified a series of metabolic reactions which, by acting as a cycle, led to the *synthesis* of urea.

The second, even more important novum in Krebs’ work was the very concept of a *metabolic cycle*: for the first time metabolic processes were shown to occur as a *cycle of reac-*

*tions*. There is no doubt that we totally owe this novel concept to Krebs – ‘obvious’ as it may look to us in 2003. Needless to say, the ornithine cycle would soon be a major stepping stone towards the formulation of the citric acid cycle and of more than 100 different cycles.

Krebs’ identification of the route of urea biosynthesis and his novel concept of metabolic cycle were immediately recognized as breakthroughs by the biochemical community of the time: he was invited to deliver lectures in Heidelberg (by Meyerhof), in Frankfurt, in Dahlem (by Max Planck on suggestion by Warburg); his name was put forward as a candidate for chairs in biochemistry; etc. Perhaps the most significant recognition came from Sir Frederick G. Hopkins, who used Krebs’ novel work as the main scientific topic in his Presidential Address to the Royal Society on November 30, 1932. This undisputed recognition was soon to provide Krebs with some shield from the hurricane that was brewing and would soon burst out and devastate nearly all Europe.

In December 30, 1932 Krebs became Privatdozent in Prof. Thannhauser’s Department. Very significantly (see more below) Prof. E. Rehn (the Dean) wrote to the Ministry of Education of the State of Baden: ‘...Dr. Krebs ‘is an excellent doctor’ ...His ‘recent scientific work, especially the paper on the synthesis of urea in the animal body, has established his international reputation. This paper is of fundamental importance and will be regarded in the future as one of the classics in medical research’.

But the winter of 1932/33 is also remembered for reasons other than the discovery of the ornithine cycle – this historical period has been called by some historians ‘the age of extremes’. Hitler seized power at the end of January 1933, making a cunning use of that skilful blend of crime, lies, blackmail and promises that had brought Mussolini to power in Italy so successfully in 1922. As we shall see, the thirties admittedly have been less dramatic to Krebs than to other Jews (or non-Nazis); still, they show how merciless, senseless and ruthless ‘simple’ discrimination and boycott can be, even if he was spared the chaotic, dramatic and convulsive last-minute boarding of a ship (like Meyerhof, in south France in 1940) and the horrors of the concentration camps. His already proven scientific value, his honesty and the decency of some friends and colleagues allowed him to take refuge in an (almost) safe haven in a relatively orderly manner. But even this had to be paid for with the parting from his family and from his German culture and Fatherland.

‘On 12 April (Krebs recounts in his autobiography [1]) I received a curt, formal, impersonal letter from the Dean of the Faculty... Prof. E. Rehn, officially informing me that at the request of the Ministry of Education, I was to consider myself on immediate leave of absence:

*Notification of immediate removal from office*

By order of the Office of the Academic Rector I hereby

E-mail address: [semenza@bc.biol.ethz.ch](mailto:semenza@bc.biol.ethz.ch) (G. Semenza).

inform you, with reference of the Ministerial Order A No. 7642, that you have been placed on leave until further notice.

Less than four months earlier this same Rehn had signed the letter which, in glowing terms, had recommended my appointment as teacher in the Medical Faculty' (see a part of this letter above, Note of the Editor).

'The Dean was implementing the following order from the Minister of Education:

*'Maintenance of Security and Order.* The Minister of Interior has decided that all members of the Jewish race (irrespective of their religion) who are employed in the service of the State in teaching establishments will be placed on leave of absence until further notice....'

This was followed on 18 April by official confirmation of my dismissal on 1 July 1933:

'I am instructed by the Minister of Education to inform you that you have been relieved of your post in connection with the Law of Reconstruction of the Professional Civil Service. Your contract will terminate on 1 July 1933.... Eitel'

The signature was that of the Administrative Director of the Hospital, a man whom I knew quite well. His son and I had recently collaborated on a paper' ...

Krebs was soon to experience that more and more of his acquaintances would show their cold shoulders; and of course he could not proceed with research.

'On 13 April I cycled to St. Peter, a small resort in the Black Forest... The fierceness of Hitler's anti-Semitic policies ...was much more severe than most of us had anticipated...' ...A young German doctor, Walter Herkel, who was spending a year in Barcroft's laboratory at Cambridge, wrote me from there on 8 April: '...I heard this morning of the misfortunes which you are sharing with many colleagues.... And I spoke immediately to Sir F.G. Hopkins, President of the Royal Society, who ...holds you in great esteem.... He said he would 'be delighted to have you here' and will talk with the Vice-Chancellor within the next few days...'

Albert Szent-Györgyi, who visited Cambridge at that time, wrote Krebs: 'If you really would like to go to Cambridge it would be best if you wrote to Hopkins and assured him that you would be content with a modest livelihood. There are no senior jobs and people might perhaps hesitate to offer anything less.... If you wish you may mention that I have encouraged you to write.' ... Naturally I took up Szent-Györgyi's suggestion and wrote to Hopkins by the next post: '...As a Jew I am about to lose not only my present position, but any possibility of working at all in Germany.... I would consider myself most fortunate if I could continue my work in your laboratory. I will, of course, be content with a modest livelihood if it means that I can carry on with my research...'

Although Hopkins was very positive, there were a number of financial hurdles to overcome; in the meantime, other prominent scientists volunteered to help this gifted young Jewish man in this most critical moment: Warburg (Dahlem), Knoop (Tübingen), Löffler (Zürich), Lambert (of the Rockefeller Foundation, who indicated the probability of funding Krebs' research in Cambridge for a year), Peters (Oxford). In the thirties money for education and science was scarce everywhere in Europe, the UK included.

'Meanwhile the political atmosphere around me was deteriorating. Posters addressed to German university students, bearing the following manifesto, appeared all over Freiburg:

*Im Rahmen einer Gesamtkaktion:*

*WIDER DEN DEUTSCHEN GEIST*

*As a part of the New Order:*

*AGAINST THE UN-GERMAN SPIRIT*

Language and literature are rooted in the people. The German people bear the responsibility to ensure that their language and literature are a pure and uncontaminated expression of their national character....

(1) Our most dangerous adversary is the Jew and he who is his vassal.

(2) The Jew can think only as a Jew. If he writes German, he lies. The German who writes German, but thinks un-German is a traitor. The student who speaks and writes un-German is, moreover, shallow and perfidious....

(7) We want to respect the Jew as an alien, and we want to take national character seriously. We therefore demand the Censor that

- Jewish works be published in the Hebrew language
- If published in German, it must be made clear that they are translations...

The Students of Germany'

This small sample of partial translation (the German text is even more weird and hysterical) should not be taken as a joke or dismissed with a good laugh. (Besides, I remember similar texts in Fascist Italy after 1938.)

'The Rector of the University, von Möllendorff ... ordered the removal of such posters from the University premises. He was immediately relieved of his office and was replaced ... by the famous Martin Heidegger, who had an international reputation as a distinguished philosopher.... He was an enthusiastic supporter of Hitler, hailing him on behalf of the University as a savior, and pledging himself to unswerving loyalty.

Heidegger's lack of political acumen is illustrated by the following documents' (of which I report only the partial translation of one, Note of the Editor):

*German Students*

The National Socialist revolution has brought about a catharsis of our German existence.... It is expected of you that you will seek out fellow thrusters and the most deeply dedicated, and expose yourself to their ideas....

The Führer, himself and alone, is the present and future German reality and law....

Heil Hitler! Martin Heidegger, Rektor

Together with Freiburg's Oberbürgermeister and the Führer der Studentenschaft, Rektor Heidegger sent Hitler the following

*'Affirmation of Loyalty*

To the savior of our nation in its crisis: from schism and dilemma of unity, resolution and honor; to the master and fighter for a new spirit of self-reliance in the community of the people, pledge unswerving loyalty the citizens, the students and teachers of the university town in the farthest south-western German borderlands.'

Krebs reports several other examples of collapse of all standards of decency – even in people till then regarded as civilized, cultivated Germans – towards fully 'integrated' German Jews, with whom they shared the same culture, literature, music, art and Weltanschauung; they shared the love for the same Fatherland, also for its integrity, sense of duty, reliability, and moral courage.

By the middle of June 1933 Krebs left for Cambridge,

although no final decision on his position there had been reached yet.

Seventy years have elapsed since. How much have we all learned from discrimination based on ‘race’ alone? (a typical non-concept). Have those years taught us biochemistry alone? No matter how complete or (even perhaps) sincere Heidegger’s political views switched during the early forties, I must wonder, together with W. Bialas [2]: Those philosophers, who have joined the national socialism in accepting it as being so very close to their way of thinking, what have they seen in it,

what have they expected from it – for what purpose did they believe they had to contribute to it, that it was the ‘Law of their Time’, and that they willingly had to share the intellectual responsibility for it?

## References

- [1] Krebs, H.A. (1981) *Reminiscences and Reflections*, Clarendon Press, Oxford, 298 pp.
- [2] Bialas, W. and Gangl, M. (Eds.) (2000) *Intellektuelle im Nationalsozialismus*, Verlag Peter Lang, Frankfurt a.M., 364 pp.