Editorial

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Lothar Jaenicke and C_1-metabolism: his first 25 years of research

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Abstract: The biochemist Lothar Jaenicke died on 29 December 2015, aged 92 years old. The last time I saw him was at his 90th birthday on 14 September 2013, at the occasion of which his colleagues at the Universität zu Köln (Cologne) in Germany had organized a symposium to honor him.

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The biochemist Lothar Jaenicke died on 29 December 2015, aged 92 years old. The last time I saw him was at his 90th birthday on 14 September 2013, at the occasion of which his colleagues at the Universität zu Köln (Cologne) in Germany had organized a symposium to honor him. Lothar Jaenicke had suggested me as one of the speakers, and I talked about C_1-metabolism, how methane is formed from CO_2, how methane is anaerobically oxidized to CO_2 by microorganisms, and how flavin-based electron bifurcation allows these processes to be coupled with energy conservation [1]. After my talk Lothar Jaenicke was one of the most active discussants. For insiders the interest of Lothar Jaenicke in C_1-metabolism was not a surprise knowing that in the first 25 years after his PhD in 1948 with Hans Meerwein he had worked on C_1-metabolism unraveling the function of folic acid, how this coenzyme – after reduction to tetrahydrofolate (H_4F) – is involved in formate activation and in purine, serine, and methionine biosynthesis. This very productive period ended in 1973 with a comprehensive review on "The biosynthesis of methionine" [2].

I will only discuss this "C_1-period" of Lothar Jaenicke's research considering that his excellent work on algal sexual attractants and morphogenesis (1970–1998) will be the main subject of the contribution of Hans Hummel and Simone Langner [3]. After his official retirement in 1988 Lothar Jaenicke wrote many brilliant profiles of German biochemists [4] and cell biologists [5] living in the first half of the 20th century, most of which, between 1999 and 2008, were originally published in the journal *BIOspektrum*, which he had cofounded in 1994.

I first met Lothar Jaenicke in 1969 when he gave a seminar on the role of folates in C_1-metabolism in *Escherichia coli* and yeast at the Biochemische Institut in Freiburg headed by Karl Decker and Helmut Holzer. At that time Kurt Jungermann and I, both postdocs in the group of Karl Decker, were investigating the synthesis of C2 and C8 of purines, C3 of serine, and the methyl-group of methionine in Clostridia and discovered that they were all derived from CO_2 incorporated via formate and probably N^{10}-formyl-H_4F, N^5,N^{10}-methylene-H_4F and N^5-methyl-H_4F as intermediates. In *E. coli* and yeast, CO_2 was known to be not a precursor of formate [1]. We discussed these interesting results with Lothar Jaenicke at the "Nachsitzung" that followed his seminar, and ever since then we stayed in close contact and over the years became scientific friends.

Lothar Jaenicke was born on 14 September 1923 in Berlin. His father, Johannes Jaenicke (1888–1984) [6], was a chemist working between 1916 and 1925 in Berlin together with Fritz Haber on the recovery of gold from sea water [7–9]. Haber won in 1918 the Nobel Prize in Chemistry for his ground-breaking work on N_2 reduction with H_2 to NH_3. Lothar's mother was Erna Buttermilch (1895–1961) [6]. In 1925 the Jaenicke family moved to Frankfurt/Main, where father Jaenicke took a leading position at the Metallgesellschaft. In 1941, after finishing high school in Frankfurt, Lothar Jaenicke began studies of botany, medicine, and chemistry in Marburg. He interrupted these studies to work for 2 years (1943–1945) as a chemical laboratory assistant at the Schering AG in Berlin. After the end of World War II he resumed his studies in medicine and chemistry in Marburg. He first concentrated on medicine since one of the few buildings in Marburg that had been destroyed in the last year of the war was the Institute of Chemistry in the Bahnhofstraße 7. In 1947 he completed his theoretical studies in medicine with the Physikum and in 1948 his chemical studies with a diploma and a PhD thesis entitled "Über die Polymerisation des Tetrahydrofurans mit Mischungen von Metall- und Nichtmetallhalogeniden" under the supervision of the famous Hans Meerwein, who held the Chair

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in Organic Chemistry at the Philipps-Universität Marburg since 1929, from which he retired in 1952 [10]. It was also in the Institute of Chemistry that Lothar Jaenicke met his later wife Doris. He married her in 1949 and they stayed together until 2005, when she died. They had four children, who mourned at his funeral on 22 February 2016 [11, 12].

Since 1944 one of Meerwein's assistants in Marburg was Karl Dimroth, who was interested in the structure of nucleic acids. After his PhD, Lothar Jaenicke joined his group to work together with him on the composition of RNA and DNA, which fascinated him more than the polymerization of tetrahydrofuran. In 1949 Karl Dimroth had taken over the Chair of Physiological Chemistry in the Medical Faculty of the Philipps-Universität Marburg, and in 1952, after a short stay as Associate Professor in Tübingen, he switched back to the chemical faculty in Marburg as successor of Hans Meerwein.

In the early 1940s it was still widely assumed that nucleic acids were built up of repetitive tetranucleotide units composed of G-C-T-A-G-C-T-A and so on (DNA) and G-C-U-A-G-C-U-A and so on (RNA). Most of the structural studies were performed with nucleic acids isolated from yeast and animal cells, which were thought to be composed of almost equal molar amounts of G, C, T, and A. The nucleotide compositions were based on analyses that were not very accurate, which is why the "tetranucleotide" hypothesis was questioned [13, 14]. In the light of this situation Dimroth and Jaenicke felt it necessary to develop novel methods to quantitatively hydrolyze the nucleic acids into nucleosides or nucleotides and to then determine these quantitatively, after separation either by paper chromatography or paper electrophoresis. The first of six papers on the subject was submitted on 28 November 1945 but – because of the war aftermath – published only in 1950 [15]. The last of the series was published in 1952 [16–20], 1 year after Erwin Chargaff published the rule that in DNA G matches C and A matches T [21]. Considering that Oswald Avery together with Colin MacLeod and Maclyn McCarty had found the hereditary units (genes) to be composed of DNA in 1944 [22] and that Francis Crick and James Watson published their double-helical model of the structure of DNA in 1953 [23], Lothar Jaenicke had definitely proven a very good instinct in what is interesting in current biochemistry when he chose to study the structure of nucleic acids with Karl Dimroth after his PhD in 1948.

The work with nucleic acids aroused the interest of Lothar Jaenicke in the biosynthesis of their components, especially of the purines adenine and guanine. Together with Karl Dimroth and E. W. Becker he showed in 1952 using 3-^{13}C-labeled serine that purine biosynthesis involves serine as precursor, C2 and C8 of the purines (Figure 1A) being

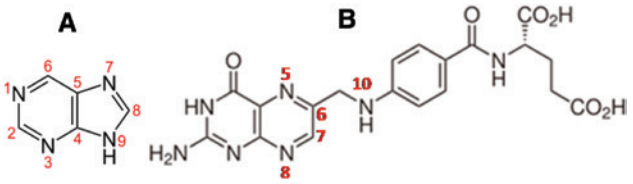

Figure 1: Structures (A) of purines and (B) of folic acid (Vitamin B9). The folic acid was isolated in 1941 [24] and its structure confirmed by synthesis in 1945 to be pteroylglutamic acid [25]. Natural folates usually differed from pteroylglutamic acid in three respects: (i) additional glutamate residues ("polyglutamates"), (ii) reduction to 7,8-dihydrofolate (H_2F) or 5,6,7,8-tetrahydrofolate (H_4F), and (iii) additional single carbon units attached to N^5 or N^{10} [26].

derived from C3 of serine [27, 28]. Together with Herrmann M. Rauen he provided evidence in 1953 that folic acid (Figure 1B) was required in the transfer of C3 from serine into the C_1 positions of the purines [29]. H. M. Rauen was a biochemist in the Physiologisch-Chemisches Institut in Marburg whose interest in folic acid was initiated in 1950 by the question whether xanthopterin (2-amino-6, 8-dioxy-pteridin) in urine of humans is a degradation product of folic acid (pteroylglutamic acid). Rauen later got to be well known by his "Biochemisches Taschenbuch" [30], which was for many years on the shelf of every biochemist in Germany.

Rauen and Jaenicke reported in 1953 [29] that N^{10}-formyl-tetrahydrofolate (N^{10}-formyl-H_4F) is an intermediate in purine biosynthesis from serine and that N^{10}-formyl-H_4F can also be formed from formate and 5,6,7,8-tetrahydrofolate (H_4F) in an ATP-dependent reaction. In analogy to the "activated acetic acid" (acetyl-CoA), Lothar Jaenicke referred to N^{10}-formyl-H_4F as "activated formic acid". He subsequently showed that N^5-formyl-folic acid can be converted to N^5-formyl-H_4F (citrovorum factor) by reduction with reduced pyridine nucleotides and N^5-formyl-H_4F converted to N^{10}-formyl-H_4F by activation with ATP. Evidence was presented that the formyl group of N^{10}-formyl-H_4F is in equilibrium by an oxidation-reduction system with C_3 of serine through a hydroxymethyl level derivative and that N^5-formyl-H_4F is not directly involved in the interconversion [31].

These results are described in the habilitation thesis of Lothar Jaenicke entitled "Die Rolle der Tetrahydrofolsäure als Cofaktor des Einkohlenstoff-Stoffwechsels" (the role of tetrahydrofolate in C_1-metabolism), which was accepted by the Faculty of Chemistry in Marburg in 1954. One year later, when Lothar Jaenicke was for 2 years at the Case Western Reserve University in Cleveland, he published the most important results of his habilitation thesis in *Biochimica et Biophysica Acta* [31]. By this publication, written in English, the scientific world got to know that in postwar Germany there was a group contributing significantly

to the understanding of the then still unknown biochemical function of folic acid in C_1-metabolism. Folic acid had been discovered in 1931 by Wills [32], who found that a factor present in yeast was able to correct a type of anemia in human pregnancy called "macrocytic" anemia and since then was of high medical interest. The paper of Lothar Jaenicke was cited in a short time 75 times, which in the mid-1950s was exceptionally high for a biochemical paper published by a German.

Because of his results Lothar Jaenicke obtained a National Research Council Fellowship (Marschall Plan Stipendium) to work for 2 years (1954–1956) at the Case Western Reserve University where in the Department of Biochemistry, School of Medicine, several groups were interested in C_1-metabolism, amongst them the groups of Harland G. Wood [33], Marvin Utter [34], W. Sakami [35], and G. Robert Greenberg [36]. In the neighboring Department of Microbiology there was Lester Krampitz working amongst others on the fixation of formate into pyruvate in *E. coli* [37]. Lothar Jaenicke teamed up with Robert Greenberg to characterize the ATP-dependent reaction leading from formate and H_4F to N^{10}-formyl-H_4F in liver extracts. The "formylase" reaction was found to yield ADP and phosphate as products in stoichiometric amounts (reaction (1)) [38]. A focus of the paper was to prove that really N^{10}-formyl-H_4F rather than an isomer was the product formed. Four lines of evidence were presented: (i) the compound "transfomylated" to 5-amino-4-imidazolecarboxamide-5′-phosphoriboside to form inosine-5′-phosphate in the absence of ATP; (ii) the compound could be converted quantitatively to the N^5, N^{10}-imidazolinium derivative; (iii) the compound was oxidized to one having the properties of N^{10}-formyl-H_2F; and (iv) the compound could be chemically converted to N^5-formyl-H_4F [38]. Also, this 1955 publication became, in its time, a citation classic.

$$\text{Formate} + H_4F + \text{ATP} \rightleftharpoons N^{10}\text{-formyl-}H_4F + \text{ADP} + \text{phosphate}. \quad (1)$$

It happens to be that 15 years later I also worked in the Department of Biochemistry in Cleveland. In the 3 months in 1991 that I was there I studied the reduction of CO_2 to formate in acetogenic bacteria with Harland G. Wood [39, 40]. He, Lester Krampitz, W. Sakami, and Marvin Utter could still remember the time that Lothar Jaenicke was there and were full of respect for his analytical thoroughness and intellectual power.

Middle of 1956 Lothar Jaenicke returned from Cleveland to Marburg to stay there only until the end of the year, because he had accepted the position of a "Privatdozent" (Assistant Professor without tenure) at the Institute for Biochemistry of the University Munich, where Feodor Lynen (Nobel Prize 1964) was director and where Lothar Jaenicke stayed from 1957 to 1962. In Munich Lothar Jaenicke continued to study the tetrahydrofolate formylase (reaction (1)) [41]. The enzyme was purified from various sources, and with the purified enzyme the mechanism was studied. The back reaction, the phosphorylation of ATP from ADP and phosphate driven by the hydrolysis of N^{10}-formyl-H_4F to formate and H_4F was of special interest because it represented a novel mechanism of ADP phosphorylating [42–45].

Lothar Jaenicke also partially purified the two enzymes catalyzing reactions (2) and (3) leading from C_3 of serine to N^{10}-formyl-H_4F [46]. Also, the biosynthesis of folic acid was studied. 7,8-Dihydrofolic acid was shown to be formed from p-aminobenzoyl-glutamic acid and 6-hydroxymethyl-2-amino-4-hydroxy-dihydropterin (HAH-dihydropterin) in an ATP-dependent reaction [reaction (5)] [47].

$$\text{Serine} + H_4F \rightleftharpoons N^5,N^{10}\text{-methylene-}H_4F + \text{glycine} \quad (2)$$

$$N^5,N^{10}\text{-methylene-}H_4F + \text{NADP}^+ \rightleftharpoons N^{10}\text{-formyl-}H_4F + \text{NADPH} + H^+ \quad (3)$$

$$\text{HAH-dihydropterin} + \text{p-aminobenzoyl-glutamate} + \text{ATP} \rightarrow H_2F + \text{ADP} + \text{phosphate} \quad (4)$$

Besides these biochemical investigations Lothar Jaenicke developed model systems to study the mechanism of tetrahydrofolate-dependent reactions. Together with Egon Brode he published in 1959 that N,N′-diarylethylenediamine can react with formic acid to the 1,3-diaryl-imidazolium salt (analogue of N^5N^{10}-methenyl-H_4F) and with formaldehyde to 1,3-diaryl-imidazolidine (analogue of N^5,N^{10}-methylene-H_4F) and that the imidazolium salt can be converted reversibly to the imidazolidine by reduction. The redox potential was significantly affected by aromatic substituents but was in all cases much more positive than in the biological system. The formyl group of 1,3-diaryl-imidazolim salts was shown to be transferred to hydroxylamine generating formyl-hydroxamate, and the methylene group of 1,3-diarylimidazoline was transferred to basic amines but not to carboanions [48]. In a second paper Brode and Jaenicke described in 1960 [49] a model for the serine hydroxymethyltransferase reaction [reaction (2)]. They showed that in the presence of both pyridoxalphosphate and N′,N′-diaryl-ethylene-diamine, serine was non-enzymatically converted into glycine and the diarylimidazolidine in an irreversible reaction.

At the end of 1962 Lothar Jaenicke moved from Munich to the University Köln (Cologne), where he became founding director of a novel Institute for Biochemistry in the Science Faculty and where he remained until he officially retired in 1988 at the then still mandatory age of 65. When he moved to Köln he was already internationally recognized as a leading scientist in C_1-metabolism indicated by the fact that he was asked in 1964 to review the function of vitamin B_{12} and folic acids for *Annual Review of Biochemistry* [50]. In 1962 he received the prestigious Paul-Ehrlich and Ludwig Darmstaedter-Preis of the Paul Ehrlich foundation in Frankfurt, Germany.

One of his first papers from Köln was on phosphorylated models of tetrahydrofolate. The question was whether in the ATP-dependent activation of formate and H_4F to N^{10}-formyl-H_4F [reaction (1)] there would be phosphorylated intermediates, which had been proposed by others. N,N′-diaryl-ethylenediamines were reacted with phosphoroxychloride to cyclic diamidophosphates that in formate buffer were converted to N-formyl-N,N′-diaryl-ethylenediamines. Lothar Jaenicke concluded that therefore a phosphorylated folate intermediate in reaction (1) would be chemically plausible [51]. Although plausible, this was later shown by him not to be the case. Alternatively, formyl-phosphate was considered as intermediate which is why Lothar Jaenicke developed a method to synthesize this compound from formyl-fluoride [52]. However, formyl-phosphate was not active in the formylase assay (reaction (1)).

At the time before Lothar Jaenicke moved from Munich to Köln evidence had been accumulated that the methyl group of methionine was somehow derived from N^5,N^{10}-methylene-H_4. Together with W. Wilmanns and B. Rucker, Lothar Jaenicke showed in 1960 that in cell extract of pig liver formaldehyde was incorporated into the methyl group of methionine. The reaction was dependent on the presence of H_4F, NADPH, homocysteine, and ATP. Adenosine could substitute for ATP and S-adenosyl-homocysteine (SAH) for homocysteine. At high H_4F concentration the NADPH requirement was no longer seen [53]. Methyl-H_4F appeared to be an intermediate [54]. These were very confusing results.

A problem was that the specific activities of methionine synthesis in the cell extracts were very low (at most 5 nmol per min and mg protein) and decreased rapidly within a short time. Therefore, it took the Jaenicke lab in Köln, in completion and collaboration with other labs, almost 10 years to unravel how methionine in most microorganisms and in animals is actually synthesized.

In 1960, when the above mentioned results by Wilmanns, Rucker, and Jaenicke were published [53], it was not yet known that in bacteria and animals vitamin B_{12} was involved in methionine biosynthesis. Only in 1961 was it reported by the D. D. Woods lab in Oxford, England, that in *E. coli* the methyl transfer reaction was dependent on the presence of a corrinoid protein that had been purified [55]. However, the involvement of vitamin B_{12} did not come as a surprise because there had already been for a long time evidence for a synergistic effect of folates and B_{12} in curing anemia and in methionine biosynthesis, as was outlined by Jaenicke in the 1964 *Annual Review of Biochemistry* [50]. Since plants, yeasts, and some bacteria do not contain B_{12}, there is also a cobalamin-independent pathway, which was only unraveled in the late 1990s [56], long after Lothar Jaenicke retired in 1988.

A big step forward in the understanding of methionine biosynthesis was made in 1967 by Stavrianopoulos and Jaenicke [57]. They reported that they had purified the methionine synthase from *E. coli* almost 1000-fold and showed the purified cob(II)alamin-containing enzyme to catalyze the formation of methionine from N_5-methyl-H_4F and homocysteine in a reaction that was dependent on the presence of a NADH: FAD oxidoreductase reduction system and catalytic amounts of S-adenosyl-methionine (SAM) [reaction (5)]. The enzyme also catalyzed the methylation of H_4F with SAM [reaction (6)] and the methylation of homocysteine with SAM in the presence of the reducing system [reaction (7)].

$$N^5\text{-methyl-}H_4F + \text{homocysteine} \rightarrow H_4F + \text{methionine} \quad (5)$$
(dependent on SAM and reduction system)

$$SAM + H_4F \rightleftharpoons N^5\text{-methyl-}H_4F + SAH \quad (6)$$
(dependent on reduction system)

$$SAM + \text{homocysteine} \rightarrow \text{methionine} + SAH \quad (7)$$
(dependent on the reduction system)

Methyl-cob(III)alamin, bound to the enzyme, was shown to be an intermediate in all three reactions. The dependence of reactions (5), (6), and (7) on the NADH: FAD oxidoreductase reduction system was explained by the fact that the methionine synthase is only active when its bound vitamin B_{12} is in the cob(I)alamin oxidation state. In the enzyme, as purified, the corrinoid is in the cob(II)alamin oxidation state [57]. Reaction (5) was found to proceed reversibly with a free energy change of –30 kJ/mol under standard conditions [58].

The role of SAM in reaction (5) remained a matter of conjecture until Rüdiger and Jaenicke showed in 1969 [59–61] that methionine synthase, when containing methyl-cob(III)alamin as prosthetic group, was independent of

SAM in the presence of the NADH: FAD oxidoreductase reduction system [62]. The interpretation of these and other results was that the reducing system is only strong enough ($E_o' = -320$ mV) to reduce a few percent of the enzyme bound cob(II)alamin to cob(I)alamin ($E_o' < -400$ mV). In the presence of SAM these few percent are methylated, allowing the reducing system to further reduce the cob(II)alamin until 100% are methylated. Whereas the reaction of SAM with cob(I)alamin is strongly exergonic and essentially irreversible, that of N^5-methyl-H_4Fwith con(I)alamin is reversible, explaining why the enzyme cannot be reductively activated with N_5-methyl-H_4F [2].

My discussion of Lothar Jaenicke's contributions to C_1-metabolism would not be complete if I would not mention his work on dihydrofolate reductase and hydroxymethyl-thiaminepyrophosphate. 7,8-Dihydrofolate is an intermediate in tetrahydrofolate biosynthesis and a product in the thymidylate synthase reaction, which explains why dihydrofolate reductase inhibitors are good DNA synthesis and growth inhibitors. Jaenicke showed that the enzyme from yeast, which he studied in detail, had properties quite different from those of higher organisms [63–65]. Hydroxymethyl-thiaminepyrophosphate, also referred to as activated formaldehyde, was shown to be an intermediate in tartronic acid synthesis from two glyoxylic acid catalyzed by a carboligase in *Pseudomonas* growing on oxalate [66–68].

Besides his experimental contributions, Lothar Jaenicke influenced the field of C_1-biochemistry by his well-written reviews in which he meticulously analyzed what is known and what not. I already mentioned the article in *Annual Review in Biochemistry* 1963 and the review on the biosynthesis of methionine in 1973 [2]. His reviews of 1961 in *Angewandte Chemie* [69] and 1963 in the Klinischen Wochenzeitschrift [70], which I remember having read when studying biochemistry in Tübingen from 1962 to 1966, were important.

Although focused on C_1-metabolism, Lothar Jaenicke worked in the 1960s and 1970s also on many other topics of which I only want to mention the mechanism of glutamine synthetase [71–76] and on the determination of nitrogen and phosphorous in biological material [77]. The latter paper together with one on the determination of reducing sugars [78] belongs to the most highly quoted papers (>200 times) of Lothar Jaenicke's long publication list. I mention this because it illustrates best the analytical interest of Lothar Jaenicke which he had developed when he was a postdoc with Karl Dimroth analyzing the composition of nucleic acid [15–20].

After 20 years successfully working on C_1-metabolism, Lothar Jaenicke, then at the end of his forties, felt that he wanted to start something totally new. Being a broadly read scientist, his interest fell on algal sex attractants. Remember that Lothar Jaenicke started university in 1941 with botany, medicine, and chemistry. He experimentally took up this new project at the end of the 1960s while still completing the studies on methionine biosynthesis. Already in 1971 the first two papers on the synthesis and structure of the sex attractant in brown algae appeared [79, 80]. Papers on hormone initiating morphogenesis in the green algae *Volvox* soon followed [81]. A new chapter with fascinating discoveries was opened that ended only a quarter of a century later with an article on "On the structure of oxyblepharismin and its formation from blepharismin", two compounds involved in negative phototaxis in the protozoa *Blepharisma japonicum* [82]. For his contributions to algal attractants and morphogenesis he received in 1979 the Otto Warburg Medal of the German Society of Biochemistry and Molecular Biology (GBM) and in 1984 the Richard Kuhn-Medal of the German Chemical Society (GDCH).

The Richard Kuhn Medal did not prevent Lothar Jaenicke from later uncovering in one of his famous short profiles that Richard Kuhn (Nobel Prize 1938) was more than a "Mitläufer" in the Dritte Reich [83], which led to a heated public debate. In the year 2005 the GDCH decided to no longer award the Richard Kuhn Medal. For his many contributions to our understanding of how German scientists behaved and survived in the period between 1933 and 1945, Lothar Jaenicke was awarded in 2000 the Lorenz Oken-Medal of the Gesellschaft Deutscher Natuforscher und Ärzte.

There are only very few scientists that I know of who have been experimentally very successful in two completely different areas of research and who additionally had the intellectual power to "reach out" effectively to the scientific community, like Lothar Jaenicke. Chapeau!

Before I close I want to mention that I also knew Rainer Jaenicke, the brother of Lothar Jaenicke, very well. Rainer was Professor of Biophysics in Regensburg. After his retirement he moved back to Frankfurt, where we sometimes met in the opera. At these occasions we often exchanged our admiration for Lothar Jaenicke.

Rainer Jaenicke died on 26 July 2016 aged 85 years [84].

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