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This Week's Citation Classic

Krebs H A & Henseleit K. Studies on urea formation in the animal organism. *Hoppe-Seylers Z. Physiol. Chem.* **210**:33-66, 1932. [Medical Clinic, University of Freiberg, Federal Republic of Germany]

The paper reports the outlines of the pathway of urea synthesis in the mammalian liver. It shows that ornithine promotes urea synthesis like a catalyst and that citrulline, arginine, and ornithine participate in a cyclic sequence, the net effect being the formation of urea from CO_2 and two molecules of ammonia. [The *SCI*® indicates that this paper has been cited over 2,180 times since 1961.]

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"Historians of science have rated this paper indeed as a major discovery. Joseph S. Fruton wrote. 'This work marked a new stage in the development of biochemical thought. Not only was an explanation of a biochemical synthesis offered for the first time in terms of chemical reactions identified in the appropriate biological system and not merely inferred by analogy to the known chemical behaviour of the presumed reactants, but also the paper provided a clue to the organisation of metabolic path ways in living cells. This became evident in 1937

with the appearance of the Krebs citric acid cycle, whose conceptual relation to the earlier ornithine cycle was obvious.'[1]

"This work was a first attempt to study a biosynthetic process in a tissue slice. When I started, it was uncertain whether a capacity for biosyntheses was retained on slicing, a technique developed by Warburg[2]

for the study of degrada-tive processes. To provide optimal conditions for the survival of tissue slices, I devised a medium which in respect to the inorganic constituents simulated blood plasma as closely as possible.

"Older saline solutions were grossly deficient in either bicarbonate and CO_2, or magnesium or phosphate. They had been based mainly on trial and error experiments which tested the ability of saline media to maintain the beating of the isolated frog heart. The new saline was based on the conviction that the concentrations of ions in blood plasma (almost identical in all mammalian species) have evolved to be optimally attuned to organ function.

"The new medium proved in fact superior to all earlier plasma saline substitutes in biochemical, physiological, and pharmacological work. This is the reason why it is now widely used and why the paper is frequently cited.

"People often enquire about my collaborator, Kurt Henseleit. He was an able and promising medical student. Having been associated with me, and not being a Nazi, he was told by the Hitler regime that there was no future for him in academic medicine. He became a successful internist in Friedrichshafen in South Germany, where he died in 1972."

1. **Fruton J S**. *Molecules and life: historical essays on the interplay of chemistry and biology.* New York: Wiley Intcrsciencc, 1972. p. 436.
2. **Warburg O H.** *Über den Stoffwechsel der Tumoren.* Berlin: Springer, 1926. 263 p.