the psychological reactions of babies to food, and as this work develops we may find that giving babies solid foods at a time when they can not mechanically manage them is a cause of some of the adverse reactions at meal time that are so common after the first year.

Hode's discussion of virus infections reveals that research on poliomyelitis and encephalitis has been particularly fruitful. The evidence that the virus is in the stools and that flies may carry the infection is revolutionizing all concepts of the epidemiology of poliomyelitis. Nelson's discussion of tuberculosis reveals really nothing new but gives an excellent summary of modern concepts.

The discussion of endocrinology is particularly disappointing. Apparently clinical endocrinology is still far, far behind the experimental work. There seems little excuse for saying that iodine therapy of toxic goiters leads to exacerbations when continued, since most authorities agree that it merely masks the state of hyperthyroidism. Other errors and improper evaluations are present in this article.

To general biologists and perhaps practitioners, Sabin's article on toxoplasmosis will be the most interesting. He was able to give an almost complete picture of a newly recognized protozoon infection. The organism invades almost all tissues and can occur in a wide variety of hosts. The exact mode of contagion and possible reservoirs of infection have yet to be worked out. The article should enable others to diagnose the cases and thus fill in the gaps in the picture.

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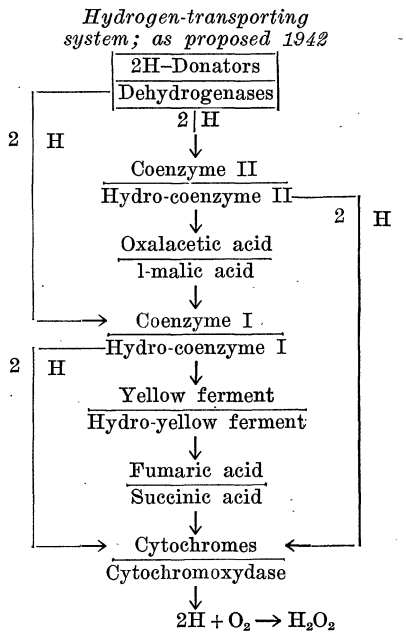
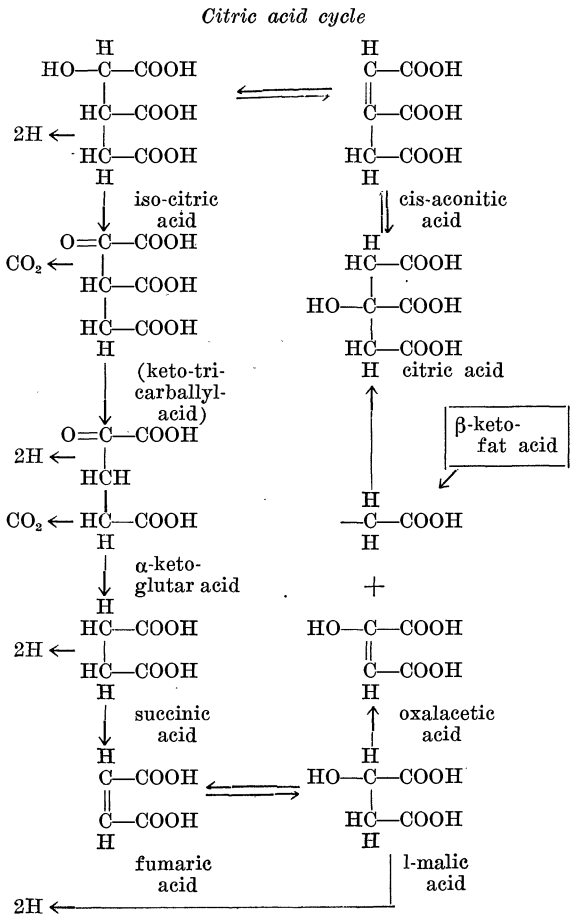
SPECIAL ARTICLES

CITRIC ACID CYCLE; SUGAR AND FAT-BREAKDOWN IN TISSUE METABOLISM

KREBS and Johnston[1] suggested the citric acid cycle to be a main link in the breakdown of carbohydrates. I contended that the citric acid was artificially produced under the conditions of their experiments.[2] I have shown that all hydrogen arising from sugar breakdown is either collected with coenzym II and from there transported to oxalacetic acid (so reduced to l-malic acid), or with coenzym I and then transported to fumaric acid (so reduced to succinic acid) and to oxygen.[3] According to Krebs' first opinion all



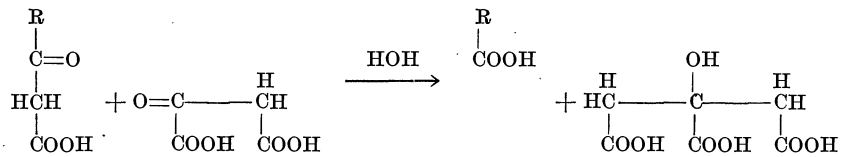


[1] H. A. Krebs and Johnston, *Enzymologia*, 4: 148, 1937.
[2] F. L. Breusch, *Zeitschr. für physiol. Chemie*, 250: 262, 1937.
[3] F. L. Breusch, *Enzymologia*, 10: 165, 1942; in print, 1943.

the carbohydrate metabolism passes over the citric acid cycle. Later on[4] he gave the cycle as accounting for only 50 per cent. of the metabolism, saying that for every cycle passed, the oxalacetic acid is reduced three times to l-malic acid. Krebs is now[5] of the opinion that no citric acid is produced, but cis-aconitic is formed by condensation of oxalacetic acid together with a sugar breakdown product. I have been able[3] to prove that in all organs the velocity of transformation of some of the essential members of the cycle, such as citric acid and α-keto-glutaric acid to l-malic acid, is only 3–10 per cent. of the velocity of the direct reduction of oxalacetic acid to l-malic acid. Furthermore, the transformation of oxalacetic acid to l-malic acid occurs in tissue also anaerobically, whilst the cycle would need large amounts of oxygen, thus definitely showing that the cycle can not play a decisive role in sugar metabolism. My views are confirmed by the work of Thomas,[6] Stare, Lipton and Goldinger,[7] Evans and Slotin[8] and Wood, Werkmann and Hemingway.[9] Perhaps the cycle takes place as a side reaction for breakdown of pyruvic acid.

I found that the pentabromacetone reaction, hitherto employed as an analytical method in all citric acid experiments, is not specific. Acetoacetic acid, always present in tissues, gives the same reaction. This defect can be avoided by five minutes boiling of acidified analytical solutions before oxidation with Br_2 and $KMnO_4$: acetoacetic acid is destroyed; citric acid remains unchanged. Thus all previous determinations (except the method of Pucher and Sherman) on citric acid require reinvestigation.

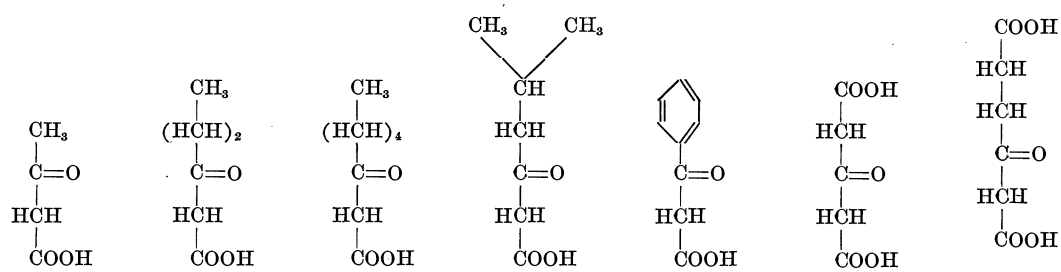
On the contrary, the cycle is the main course in breakdown of fatty acids. Thirty-eight years ago Knoop[10] discovered β-oxidation. Though much work has been done, the subsequent course of breakdown of β-keto acids could not be detected. I have discovered a new enzyme (citrogenase), catalyzing the following reaction:



n-β-keto acid + oxalacetic acid → n-2 acid + citric acid

The n-2 acid, so produced, is again β-oxidized; the citric acid is broken down over the cycle (discovered in all main reactions by Knoop and Martius[11] and Szent-Györgyi[12]) to oxalacetic acid and two mol. carbondioxide. Citrogenase is only specific with β-keto-acids, but not specific with R. It has been shown[3] that the following β-keto-acids give the same condensation-reaction.

Not only β-keto-mono carbon acids give the breakdown condensation, but also β-keto-dicarbon acids, thus showing that also β-keto-dicarbon acids after ω-oxidation of Verkade are condensed in the same way. The enzyme occurs in large amounts in muscle, kidney, brain, but little in liver and not at all in spleen, pancreas, lung, thus confirming perfusion experiments of Snapper and Grünbaum, showing that muscle, kidney and brain metabolize large quantities of β-oxybutyric acid, liver only to a small extent and spleen and lung not at all.



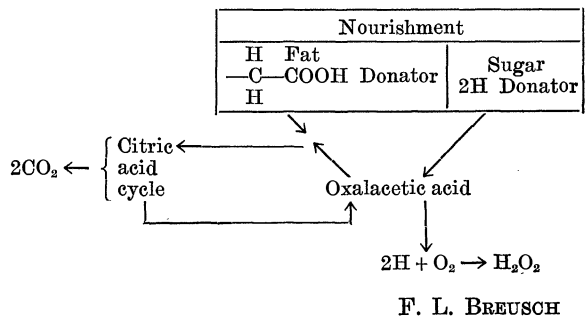
The enzyme is extractable from tissue with 0.5 per cent. $NaHCO_3$; the solution is stable for some hours. It is destroyed by boiling, is sensitive to arsenic acid, to selenic acid, partly sensitive to NaF and not at all

[4] H. A. Krebs and others, *Biochem. Jour.*, 34: 442, 462, 775, 1234, 1383, 1940.
[5] H. A. Krebs, *Biochem. Jour.*, 36: IX, 1942.
[6] Thomas, *Enzymologia*, 7: 231, 1939.
[7] Stare, Lipton and Goldinger, *Jour. Biol. Chem.*, 141: 981, 1941.
[8] Evans and Slotin, *Jour. Biol. Chem.*, 136: 301, 1940; 141: 439, 1941.
[9] Wood, Werkmann, Hemingway and Nier, *Jour. Biol. Chem.*, 139: 483, 1941.
[10] Knoop, *Hoffmeister's Beiträge*, 6: 150, 1905.
[11] Knoop and Martius, *Zeitschr. für physiol. Chemie*, 242: 1, 1935; 246: 1, 1935.
[12] Szent-Györgyi and others, *Zeitschr. für physiol. Chemie.*, 236: 1, 1935; 244: 105, 1936.

to iodacetic acid. The quantity of citric acid formed is about I–6 mg per gram wet tissue per hour at 38° C.

Oxalacetic acid is therefore the meeting point in sugar and fat metabolism. Sugar (as 2 H donator) and fat (as $-\overset{H}{\underset{H}{C}}-COOH$ donator) are in competition to metabolize oxaloacetic acid. Sugar-H is metabolized preferentially, as already small traces of sugar hydrogen reduce immediately and quantitatively small amounts of oxalacetic acid to l-malic acid, while the condensation of β-keto acids with oxalacetic acid needs a surplus of oxalacetic acid, but only small amounts of β-keto acid.

Fat is only metabolized by oxalacetic acid, if small amounts of sugar are available; if no sugar at all is available, no pyruvic acid as precursor of oxalacetic acid (perhaps formed from pyruvic acid and carbon-dioxid after Evans and Slotin) is formed. Under such conditions β-keto acids are not metabolizable and we find the normal excretion of ketoacids in urine, as happens if much fat and little sugar are given with the food. We can formulate as follows:



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A MAP OF THE NATURAL AMINO ACIDS

CHART 1 has been designed as a visual aid for those whose work or interest is concerned with the protein-building α-amino acids. One may distinguish in each amino acid the $^{+}H_3N-\underset{|}{CH}-COO^{-}$ grouping which, as the carrier of the peptide-forming and acid-base functions common to all, may be termed the "body," and the remainder of the molecule, which, because it imparts to each compound its individuality and modifies the function of the "body," can be conceived of as the "head." Crude as this distinction is—as, for instance, it takes no account of the acid or basic functions of the dicarboxylic and diamino acid—it is useful as a basis for the systematic arrangement shown. In the chart each amino acid (to the extent permitted by current knowledge) has been characterized by a few data which may be considered as of fundamental chemical and biological significance. The first column of figures in the upper left corner of each space gives, in downward order, approximate figures for the optical rotation, on a molar basis, [M], in acid, neutral (isoelectric) or basic solution. The next column gives data on the dissociation constants of the acid and basic groups, expressed in pK values of acid (—COOH, —OH, —SH, $=NH_2^+$, $-NH_3^+$) groups. In those cases where groups other than carboxyl and amino are involved their identity is indicated by a symbol wherever possible. A figure separated by a blank space at the lower end of the pK column refers to the isoelectric point (pI). A figure in the upper right-hand corner shows the solubility at room temperature, in moles per liter. The figure to the left of the name is the molecular weight. A line under the name signifies that the amino acid is one of those found nutritionally indispensable (in rat and dog) for normal growth by Rose.[1] The dashed line (arginine) indicates that this amino acid can be synthesized by the animal organism but that the rate of bio-synthesis in the rat is not adequate for the requirements of normal growth. A dotted line under the name classifies the amino acid as one of those found necessary in the diet for the maintenance metabolism of adult rats.[2]

Those familiar with the chemistry of amino acids need not be reminded that of necessity the selection of the amino acids included in the chart is to some extent an arbitrary one, and that the same holds true for the numerical data given, where the dependence of optical rotations or dissociation constants on temperature or concentration, and other variables had to be ignored in favor of approximation values. The handbook of Schmidt[3] has been the source of most of the data shown. Blank spaces in the chart suggest possible undiscovered protein components. They do, however, neither exhaust the possibilities, nor has each space a hypothetical occupant. Spaces which for obvious reasons have no structural meaning have been marked by a black dot.

The chart is presented[4] in the hope that it may be of some use to the student, investigator and practitioner in fields ranging from physical chemistry to practical nutrition.

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[1] SCIENCE, 86: 298, 1937.

[2] Burroughs, Burroughs and Mitchell, *Jour. Nutrition*, 19: 363, 1940.

[3] "The Chemistry of the Amino Acids and Proteins," Springfield, 1938.

[4] A limited number of reprints is available. A magnifying glass will aid in reading the small print.