selection of experimental data, together with the careful inclusion of experimental data in support of each conclusion presented, the authors have achieved the happy result of a book that is authoritative without being encyclopedic.

Among the best features of the treatment are the following:

(1) For each molecule whose structure is definitely known from electron-diffraction or x-ray data, the interatomic distances and bond angles have been given and a helpful scale drawing of the molecule included. For molecules whose structure must be deduced from other evidence (*e.g.*, spectra, freezing-point depression, chemical reactivity) the actual data are cited.

(2) By judicious use of tables, the authors have been able to include a wealth of physicochemical data for each compound, without interfering with the continuity of the text.

(3) About half the book is devoted to the methods of preparation and the principal reactions of the compounds discussed. In these sections the authors' physicochemical approach shows to great advantage. Each equilibrium is discussed from a quantitative, thermodynamic point of view. Numerical reaction-rate laws, or occasionally tabulated rate data, are given for almost every reaction discussed. For complex reactions (those of nitrous acid, hypophosphorus acid, or peroxydisulfate, to mention a few) the probable reaction mechanisms have been outlined.

"Systematic Inorganic Chemistry" should prove to be not only a valuable text for the graduate students for whom it was designed, and not only a reference book for any research worker who uses these inorganic compounds, but also a challenge to other inorganic chemists to write equally good books covering other parts of the periodic table.

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SPECIAL ARTICLES

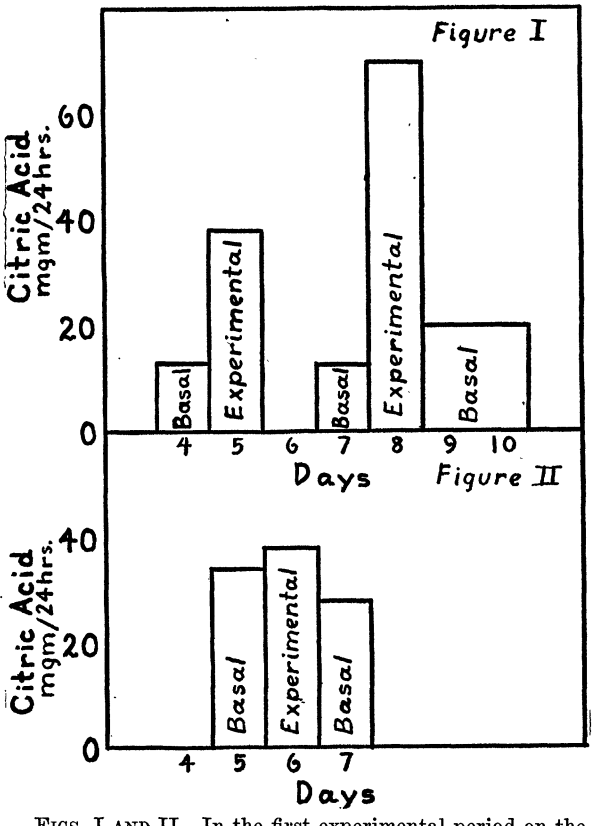
THE EFFECT OF COCARBOXYLASE ON THE CONVERSION OF FAT TO CARBOHYDRATE

IN a recent study on the conversion of fat to carbohydrate, two lines of attack suggested definite possibilities. The first arose from a realization of the fact that odd-numbered fatty acids are readily converted to glucose[1]; the second, from the apparent necessity of a catalytic reaction to increase the sugar production over that already present in an animal. Since the experimental diabetic animal produces sugar in large quantities, it was conceivable that the second approach might increase sugar output in this animal.

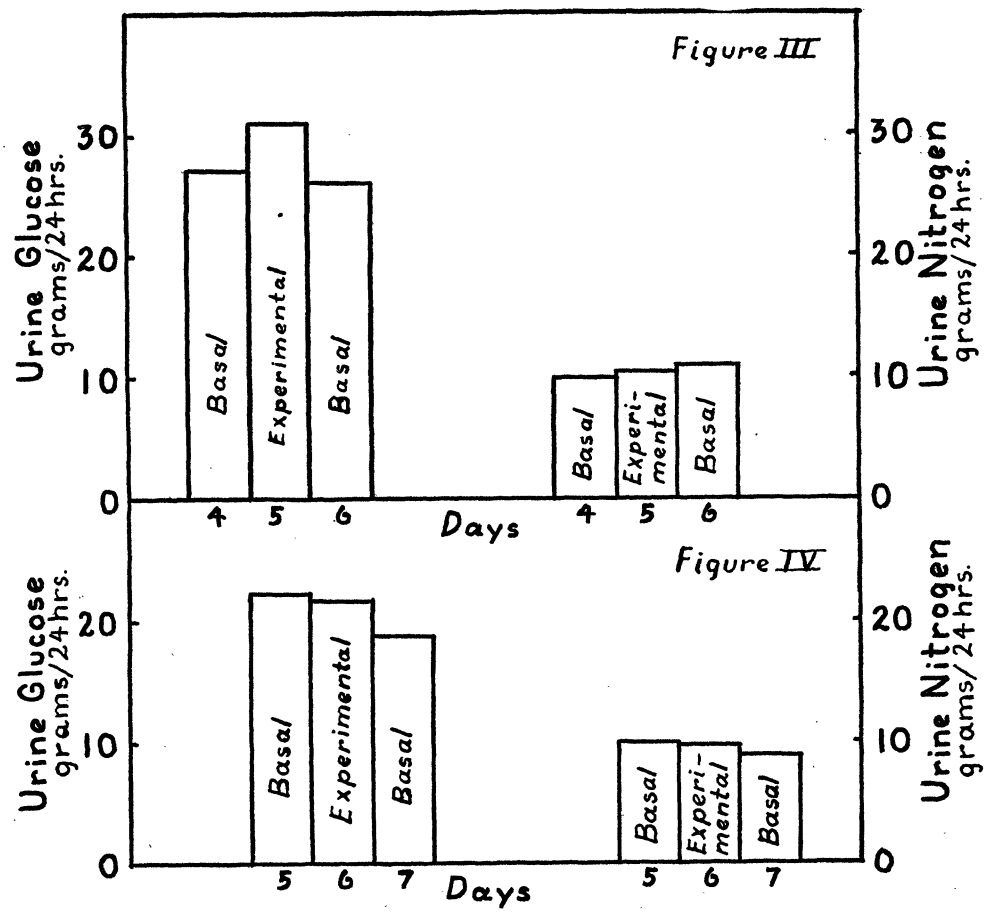
If one could cause an even-numbered carbon fatty acid chain to be converted to an odd-numbered carbon chain, the conversion should proceed from that point to glucose. The reverse reaction, in which an odd-numbered carbon acid (pyruvic) is converted to an even carbon chain, is known. The catalyst involved is cocarboxylase. Its action is believed to involve reversibly the liberation or combination of CO_2 from pyruvic and back to pyruvic.

The molecule that most closely resembles pyruvic acid and that is intermediate in the breakdown of fat is acetoacetic acid. It differs from pyruvic acid only in having one more carbon and in having the keto group in the beta position instead of the alpha. Since the alpha keto acid can form sugar, it was reasoned that the beta keto acid should, after decarboxylation, perform in a similar manner, though probably to a much less extent. It therefore seemed worth while to

[1] J. S. Butts, H. Blunden, W. Goodwin and H. J. Deuel, Jr., *Jour. Biol. Chem.*, 117–131, 1937.



FIGS. I AND II. In the first experimental period on the fifth day off insulin, 6.54 grams of the acetoacetate radical were given by stomach tube along with 32.9 milligrams of cocarboxylase. On the eighth day off insulin, 6.54 grams of the acetoacetate radical plus 33.5 milligrams of cocarboxylase again were administered by stomach tube. In the last experimental period the animal utilized 3.77 grams of the acetoacetate radical, excreting as citric acid



FIGS. III AND IV. Fig. III shows the results of giving 12 grams of citric acid plus 29.7 milligrams of cocarboxylase to a depancreatized dog by stomach tube during the experimental period. A 98 per cent. theoretical conversion to glucose was obtained. Fig. IV shows results from the same dog, given the same dose of cocarboxylase as in Fig. III, but without citric acid.

try the effect of cocarboxylase in the diabetic animal. It was, of course, realized that pyruvic acid breakdown is catalyzed by this enzyme and that carbohydrate combustion consequently might be increased, but in the totally diabetic animal this reaction would be minimal.

In most of these studies the depancreatized dog was used as the experimental animal. The fourth to sixth day off insulin, after complete healing, proved to be the best starting point.

Cocarboxylase injected intravenously was soon found to have the effect of increasing sugar excretion. Illustrative results are shown in Table 1.

Under favorable conditions the respiratory quotient (R.Q.) was lowered from the neighborhood of 0.70 to 0.59. It was lowered further, often to 0.51 (Exp. I), by the feeding of sodium butyrate to the animal treated with cocarboxylase. This change in R.Q. was brought about principally by a falling off in the CO_2 expired. Theoretical calculation showed that the assimilation of CO_2 must have taken place to account for the decreased R.Q.

Simultaneously with the lowering of the R.Q., the

only about 1.7 per cent. of the amount utilized. Data from a different dog are represented in Fig. II. Thirty milligrams of cocarboxylase alone were administered by stomach tube in the experimental period.

TABLE 1

Dog No.	I	VIII	IX	XI	XII
Basal R.Q. *	0.68	...	0.71	0.69	0.67
R.Q. after injection of cocarboxylase	0.51	...	0.65	0.60	0.59
Basal urinary glucose,† gm/hr	0.65	1.79	1.00	1.19	1.14
Experimental urinary glucose,† gm/hr	1.17	2.53	1.30	1.69	1.56
Basal D:N ratio	2.59	5.1	2.75	3.1	3.3
Experimental D:N ratio	3.33	7.1	3.67	4.0	5.7
Amount of cocarboxylase injected mg.	10	5	8	5,5,5,5	15 & 18
Sodium butyrate injected gm.	4	0	0	0	0

* The R.Q.'s were measured over a 10-minute period by the Tissot-Haldane method. The lowest values are given, as obtained in periods starting from 10 to 30 minutes after the last injection.

† Urinary glucose and nitrogen values were measured over a 1- to 4-hour period. The experimental period included the R.Q. determination.

excretion of sugar in the urine increased, and this in turn, without significant change in nitrogen excretion, caused an increase in the D:N ratio. It is impossible at present to interpret the results other than by the process of conversion of fatty acid to glucose.

An alteration in the amount of acetoacetate excreted after introduction of cocarboxylase suggested studies on the possible intermediates involved in the conversion of fat to carbohydrate. Pigeon breast muscle was found to oxidize pyruvic acid faster when treated with an extract of rat kidney cortex which had been incubated with sodium acetoacetate than when treated in the same manner without the acetoacetate, thus indicating the formation from the acetoacetate of some member of the citric acid cycle.[2]

Further investigation with acetoacetic acid showed an increased citric acid excretion in the urine from diabetic animals fed acetoacetic acid plus cocarboxylase (Figs. I and II). In line with this investigation it was found that citric acid is converted to glucose when cocarboxylase is present, but not without cocarboxylase. Actually a small amount of glucose is formed with cocarboxylase alone, but much more when both citric acid and cocarboxylase are present (Figs. III and IV).

The formation of fat from carbohydrate is therefore demonstrated. The course of the conversion is from acetoacetic acid to citric acid, or another member of the cycle, and thence to glucose. The action of cocarboxylase probably is a complicated one, but its use in the depancreatized dog clarifies the principal steps by which the conversion proceeds. Doubtless the same reactions occur in the normal subject fed high fat diets, but because insulin is present the glucose formed is for the most part immediately oxidized and therefore no change in the R.Q., or at most very small changes, are detectable.[3]

The author is indebted to Professor J. R. Murlin for his advice and criticism throughout this investigation.

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ALKALINE PHOSPHATASE IN THE OVARIAN FOLLICLES AND CORPORA LUTEA

IN a report on the distribution of alkaline phosphatase in normal tissues, made possible by an ingenious method of demonstrating that enzyme in sections, Gomori[1] called attention to the great variation in the distribution of phosphatase in the mammalian ovary. His brief remarks on the subject suggested the advisability of a more systematic study of the ovary in this respect. Because of Gomori's finding that in some species the theca interna and the membrana granulosa of the follicle differ as to their content of alkaline phosphatase, there seemed to be a possibility of tracing the fate of the theca cells in the formation of the corpus luteum, and thus of contributing to the solution of an old and by no means fully settled question.

The observations summarized herewith were made exactly according to the directions of Gomori in the paper cited, except that the period of incubation was lengthened to 2 hours. Statements as to the presence or absence of phosphatase refer only to the cytoplasm; practically all cell-nuclei contain the enzyme and any differences that may exist between them are not relevant here.

Mature follicles of the domestic pig, from sows in estrus, yield striking preparations; the cells of the theca interna are heavily laden with black granules indicating the presence of phosphatase, whereas the cytoplasm of the granulosa cells is entirely free of the enzyme. This difference persists after ovulation and during the organization of the corpus luteum, as will be explained below. Nearly mature follicles from a bitch in estrus were exactly similar to the sow's follicles.

Mature follicles from a rabbit 9 hours after mating showed, on the contrary, a strong concentration of phosphatase in the granulosa but none in the theca interna. In continuance of this condition, in corpora lutea about 8 hours, 3 days and 5 days old, respectively, the lutein cells (most or all of them derived from the granulosa) were laden with the enzyme. Gomori found no phosphatase in rabbits' corpora lutea, except in endothelial cells, but he did not state the age of the corpora lutea and possibly he studied only retrogressive corpora. Ripening follicles ca. 0.8 mm in diameter, of a guinea pig in estrus, less than 1½ hours after opening of the vaginal closure membrane, showed a heavy black deposit representing phosphatase in the theca interna, and a light deposit in the granulosa. Gomori reported the theca interna of the rabbit negative, but he probably studied only immature follicles. Three days and nine days after ovulation, and in a number of pregnant animals given me by Dr. W. L. Hard, the lutein cells were strongly positive, confirming Gomori's statement.

A recently ruptured follicle of the rhesus monkey, obtained within 24 hours after ovulation, while theca interna and granulosa were still clearly distinguishable, showed a strong concentration of phosphatase in both layers. A corpus luteum from another monkey,

[2] The author is indebted to Mr. John J. Kelly and Mr. Robert E. Gosselin, of the Department of Physiology, for their assistance in this part of the work.

[3] E. E. Hawley, C. W. Johnson and J. R. Murlin, *Jour. Nutrition*, 6:523, 1933.

[1] G. Gomori, *Jour. Cell. and Comp. Physiol.*, 17: 71–81, 1941.