the other of those two semi-circles, but it would seem that there must be other ways in which they could lie within some same semi-circumference.

In the hypothesis that a coin which comes down heads 15 times out of 20 (p. 198) be unbiassed the author considers only one tail of the distribution, *i.e.*, when there are 15 or more heads, but in the succeeding paragraph he seems to imply that we should use both tails. This seems inconsistent, but perhaps it is merely unclear to me. I am likewise troubled by the developments in pages 342–3 and in particular by the formulas 14.45 and 14.49, the former of which contains $\Gamma(n-2)$ in the denominator and the latter is for the special case when $n=2$; as $\Gamma(0)=\infty$ I have had trouble making the transition. The statement of the problem on page 367 seems unfortunately confused.

These criticisms are but trifles; Kendall's book is really a "must" for all who are concerned with advanced statistics.

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PROBLEMS IN PHYSICAL CHEMISTRY

How to Solve Problems in Physical Chemistry. By JOSEPH A. BABOR and GARRETT W. THIESSEN. 215 pages. New York: Thomas Y. Crowell Company. 1944. $1.25.

"How to Solve Problems in Physical Chemistry," by Joseph A. Babor and Garrett W. Thiessen, should prove to be a useful supplementary book for elementary students attempting to attain a working knowledge of physical chemistry. The well-organized and carefully classified sets of problems should prove useful to teachers seeking illustrative examples or graded homework exercises. The book consists of fourteen chapters each pertaining to a specific topic in physical chemistry such as gases, the solid state, thermochemistry, homogeneous equilibrium, chemical kinetics, electrochemistry, etc. The fundamental mathematical formulae pertaining to the topic, several completely worked out illustrative problems and numerous examples with answers are given in each chapter. The presentation is so lucid that the difficulties for the student are reduced to a minimum.

There is always danger that if too heavy emphasis is placed upon the working of stereotyped problems the student tends to lose spontaneity in the tackling of new problems and even tends to solve the problems in a mechanical fashion without fully understanding what is in back of the methods used. The teacher is therefore cautioned to encourage students to use their own initiative in solving problems, using the book as a guide and source of reference rather than as a crutch which when taken away will leave the student limping.

In summary, this small volume should be especially useful as a supplementary text in elementary physical chemistry, particularly for the average student.

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SPECIAL ARTICLES

THE EFFECT OF BIOTIN ON THE METABOLISM OF LIVER SLICES FROM BIOTIN-DEFICIENT RATS

DURING the course of the program of investigation into various phases of the biological significance of biotin which has been in progress in this department for the past few years, opportunity has been afforded us of carrying out *in vitro* studies on the respiratory metabolism of tissues from biotin-deficient animals. Certain of these studies have yielded results of considerable interest which we wish to summarize here.[1]

Specifically, we have found that small amounts of biotin added to slices of biotin-deficient rat liver respiring in Ringer-bicarbonate solution containing either lactate or pyruvate as substrate produce a significant effect on the metabolic processes of the tissue, as evidenced by both chemical and manometric data. The manometric data were obtained with the differential manometer of Summerson,[2] which permits measurement not only of oxygen consumption but also of the respiratory quotient and of bicarbonate decomposition ("acid formation") or, equally well, bicarbonate production. This latter is of particular significance in the present connection.

The nature of the effect of added biotin on the respiratory metabolism of biotin-deficient liver slices is indicated by the data of Table 1, which presents results from a number of experiments typical of the many which have been run. It can be seen that in the presence of lactate, there is usually (but not invariably) a slight rise in both the oxygen consumption and the R.Q. on the addition of biotin, but in neither instance is the change striking.

In every case, however, the presence of added biotin is associated with a marked change in the aerobic Q_G value, the so-called "aerobic glycolysis." This change is always in a negative direction, the Q_G value becoming either less positive or more negative in the presence of biotin. Since conventionally a positive Q_G value represents acid production (bicarbonate decom-

[1] This work was supported in part by grants from The National Cancer Institute.

[2] W. H. Summerson, *Jour. Biol. Chem.*, 131: 579, 1939.

position), a change in the opposite direction corresponds to either an inhibition of acid production, an increased production of bicarbonate or both. Further study has revealed that a major factor in the biotin effect is an increased production of bicarbonate, due to an increased utilization of lactate. This is evident from the data in the last column of Table 1, which

TABLE 1

THE EFFECT OF BIOTIN ON THE METABOLISM OF BIOTIN-DEFICIENT RAT LIVER SLICES IN THE PRESENCE OF LACTATE

Experimental conditions: 25–35 mg dry weight liver tissue in 2.2–2.4 cc Ringer-bicarbonate medium containing 0.005 M–0.02 M sodium *dl*-lactate. Gas phase: 95 per cent. O_2–5 per cent. CO_2. Temp., 38° C. Biotin concentration (when present): 1 microgram per cc of medium.

Animal No.	Diet	Liver biotin content γ/gm	Added biotin	Q_{O_2}	R.Q.	$Q_G^{O_2}$	$Q_{LA}^{O_2}$
7	B	0.8	+	−4.9	0.79	−0.15	−1.03
			−	−4.6	0.74	0.60	−0.76
42	B	0.2	+	−7.1	0.98	−0.72	−1.53
			−	−6.5	0.92	0.06	−1.23
70	B	0.1	+	−7.3	0.91	−0.78	.....
			−	−6.6	0.94	−0.31	.....
81Y	EW	0.9	+	−5.7	0.87	0.26	−1.00
			−	−5.9	0.81	0.60	−0.80
84Y	EW	0.6	+	−10.2	0.68	−2.33	.....
			−	−9.8	0.59	−1.34	.....
72Y	EW	0.3	+	−10.9	0.79	−3.53	.....
			−	−11.2	0.77	−2.32	.....

The symbols Q_{O_2}, R.Q., and $Q_G^{O_2}$ have their usual significance, $Q_{LA}^{O_2}$ refers to lactic acid values determined by chemical analysis and expressed in the same units as $Q_G^{O_2}$. Diet B contains 10% egg white and 0.1% "butter yellow." Diet EW contains 40% egg white and no "butter yellow."

gives the results of chemical analyses for lactate utilization, using the method of Barker and Summerson.[3] It is clear that added biotin results in a 25 per cent. to 35 per cent. increase in the rate of disappearance of added lactate; increases up to 50 per cent. or more have been occasionally observed. The production of bicarbonate which is measured on the manometer is due of course to the sodium remaining after the lactate has been metabolized.

When pyruvate is used as substrate, the manometric picture is quite similar to that described for lactate. Added biotin usually produces a slight rise in oxygen consumption and in the R.Q.; the effect on the Q_G values is invariably as striking as for lactate. There is no effect of added biotin when glucose is the substrate or when a non-nutrient medium is used.

About 30 minutes' incubation of the liver tissue with biotin is required before the effect of biotin becomes significant. As little biotin as 2 parts in ten million of medium have been found to have a demonstrable influence on the metabolism of the liver. Other tissues from biotin-deficient animals which have been studied include heart and brain; for neither of these could an effect of added biotin on metabolism be demonstrated, although livers from the same animals gave satisfactory results.

The analyses for the biotin content of the livers used are expressed on a dry weight basis and were run for us by Dr. Karl Dittmer and Mrs. Glenn Ellis, to whom we wish to express our appreciation. The yeast-growth method of assay was used. Normal rat livers assay from 2 to 4 micrograms per gram dry weight by this method.

Our first biotin-deficient rats came from a group which was on a biotin-low synthetic diet containing, in addition to the usual ingredients, 10 per cent. egg white, a high riboflavin content and 0.1 per cent. "butter yellow" (diet B of Table 1). The livers from these animals were essentially normal except for their low biotin content, but interpretation of our results was complicated by the presence of "butter yellow" in the diet. The experiments were therefore repeated on rats rendered biotin-deficient by a synthetic diet containing no "butter yellow" and from 30 per cent. to 40 per cent. egg white (diet EW in Table 1). No differences were noted between the two groups of animals with regard to the effect of added biotin on the respiratory metabolism of the liver slices.

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[3] S. B. Barker and W. H. Summerson, *Jour. Biol. Chem.*, 138: 535, 1941.

10-NOR-PROGESTERONE, A PHYSIOLOGICALLY ACTIVE LOWER HOMOLOG OF PROGESTERONE

ESTROGENIC activity is to a great extent independent of specific chemical structures and configurations. Syntheses have yielded a number of active estrogens which are structurally only slightly, if at all, related to the naturally occurring hormones. No comparable synthetic compounds exist in the field of androgenic, progestational and adrenal-cortical hormones. It appears that progestational and adrenal-cortical activities depend on fairly specific chemical structures and configurations.

The question arises, at what stage simplifications in the structures of the naturally occurring hormones are accompanied by the loss of physiological activity. With this problem in mind 10-nor-progesterone was prepared. In this compound the angular methyl group at C_{10} is replaced by hydrogen. This structure resembles closely that of progesterone in that the characteristic side chain is left unchanged.

The 10-nor-progesterone was prepared by a series of chemical transformations starting with strophanthin.[1]

[1] Maximilian Ehrenstein, *Jour. Org. Chem.*, Vol. 9, No. 5, September, 1944.