on both diets (Table I). A significantly greater* amount of creatine was excreted by the animals on the diets deficient in methionine and choline on the 8th and possibly the 12th days only. This increased excretion of creatinine at the start, and of the creatine later, appeared to be associated with the time when the animals were losing weight. Generally an increased creatine excretion was associated with a weight loss in the individual animals whenever it occurred during the experimental period. The differences in creatine and creatinine excreted by the 2 groups were not significant during the latter part of the period when the animals on the low protein diet maintained their weight or gained slightly.

The excretion of similar or greater amounts of creatine or creatinine by the animals on the diet deficient in methionine and choline for lipotropism, gives no indication of a deficiency of methyl groups for creatine formation. This again suggests that there is a preferential use of labile methyl groups for creatine formation associated with the demand for growth. Apparently there is no conservation of the deficient supply of methyl groups during the time fatty livers are developing in these animals, but actually a wastage due to the increased creatine or creatinine excreted when the fed animals are losing weight. The general constancy of the creatinine excretion is in line with the finding of Borsook and Dubnoff[7] that under physiological conditions the phosphocreatine spontaneously yields 2% of free creatinine and that its excretion does not characterize any active process in the tissues. The increased creatinine excretion during the early part of the test period was probably due to a readjustment of the body fluids to the new dietary conditions. The loss of weight involving muscle tissue would explain the increased creatinuria.

Summary. No diminution in the formation of creatine, as measured by its urinary excretion, was found in animals on a diet deficient in labile methyl groups. The available methionine was preferentially used for growth and creatine formation. The increased excretion of creatine by these animals, apparently associated with weight loss, causes a waste of needed methyl groups instead of their conservation.

Grateful acknowledgment is made to Dr. C. R. Treadwell for his generous advice.

* Apparent differences were analyzed for significance by the *t* method of Fisher, R. A., *Statistical Methods for Research Workers*, 7th edition, Edinburgh, 1938. Only those showing a *P* value of 0.01 or less were considered significant.

7 Borsook, H., and Dubnoff, J. W., *Annual Review of Biochemistry*, 1943, **12**, 187.

15474

Urinary Secretion of Acetone Bodies in Diabetic Ketosis.

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It is generally recognized[1] that the urine from a patient with diabetic coma, occasionally, may give a negative test for diacetic acid with ferric chloride, and only a mild reaction for acetone bodies with nitroprusside. The studies of Widmark,[2] and Briggs and Shaffer[3] indicated that acetone passes into the urine and expired air by the simple process of diffusion. If this is true, then the concentrations of this fraction of the acetone bodies in the blood and urine should always

1 Joslin, E. P., Root, H. W., White, Priscilla, and Marble, A., *The Treatment of Diabetes Mellitus*, seventh ed., Lea and Febiger Co., Philadelphia, 1940.

2 Widmark, E. M. P., *Biochem. J.*, 1920, **14**, 364.

3 Briggs, A. P., and Shaffer, P. A., *J. Biol. Chem.*, 1921, **48**, 413.

TABLE I.
Concentrations of Acetone Bodies in Blood and Urine from Patients with Diabetic Ketosis.

	Blood Quantitative mg %			Urine				
				Quantitative mg %		Qualitative		
Case No.	Acetone	Total acetone bodies	Glucose	Acetone	Total acetone bodies	$FeCl_3$	Nitro-prusside	Sugar (Benedict's)
1	23.7	90.6	889	22.2	319.2	+++	++++	++++
2	21.5	94.0	507	27.8	436.5	+++	++++	++++
3	25.6	114.0	680	26.2	63.0	Neg.	++	++++
4	29.4	91.0	478	29.7	86.0	Neg.	++	++++
5	33.2	111.0	641	37.6	741.0	++++	++++	++++
6	5.8	28.1	358	5.1	63.3	+	+++	++++
7	6.5	29.6	484	7.7	72.1	++	+++	++++
8	3.0	9.2	390	2.8	36.4	Neg.	+++	++++
9	1.9	4.9	306	2.0	15.2	Neg.	+	++++
10	1.2	5.2	320	1.2	17.8	Neg.	++	++++
11	1.8	3.9	310	2.2	14.8	Neg.	++	+++
12	1.2	3.0	253	1.4	10.6	Neg.	+	+++

be similar; and this relationship should not be influenced by any disturbance of kidney function nor by decomposition of diacetic acid within the urinary passages. However, it has been reported by Martin and Wick[4] that there is no definite relation between the concentrations of acetone in blood and urine with diabetic acidosis; they were inclined to doubt the accuracy of the methods used in early work on the excretion of acetone.

The recently devised method of Greenberg and Lester[5] is especially adapted to the study of this problem, since acetone is determined directly in the presence of diacetic acid. This method was employed in the present study. The volumes of reagents and samples were increased five-fold so that 10 ml of CCl_4 extract were obtained for reading in the Evelyn instrument. Digestions for total acetone were conducted under a condenser with ground glass connections.

Results are presented in the accompanying table of the work done on the admission specimens from a group of patients with diabetic ketosis; the first 5 cases were patients with diabetic coma.

Inspection reveals that the concentrations of acetone in blood and urine are consistently similar. These results, therefore, tend to support the view that acetone is excreted into the urine by the physical processes of filtration and diffusion. This view is also supported by the study of Lehman,[6] which has just appeared. He found similar concentrations of acetone in blood and urine following the intravenous administration of iso-propyl alcohol. Probably the failure of Martin and Wick to observe this relation was due to the fact that what they studied and reported as "acetone" was the fraction of the total acetone bodies precipitated by boiling with mercuric sulfate; this fraction represents acetone plus diacetic acid. It was pointed out by Widmark that the excretion of these 2 substances follows entirely different laws.

Two instances of diabetic coma with "renal block" are provided by Cases 3 and 4. In each case the total acetone body content of the urine was actually less than that of the blood; in each case the urinary test with ferric chloride was negative and that with nitroprusside only 2+. Since the concentrations of free acetone in blood and urine are similar, it would appear that either diacetic or oxybutyric acid is excessively reabsorbed by the renal tubules; the negative reaction with ferric chloride implicates diacetic acid. (The assumption is made that decomposition of diacetic acid in a slightly acid medium, during the flow through the urinary passages,

[4] Martin, Helen E., and Wick, A. M., *J. Clin. Inv.*, 1943, **22**, 235.

[5] Greenberg, L. A., and Lester, D., *J. Biol. Chem.*, 1944, **154**, 177.

[6] Lehman, A. J., PROC. SOC. EXP. BIOL. AND MED., 1946, **62**, 232.

is not an important item).

These observations, therefore, indicate that the nature of the renal block is something of a functional disturbance due to an alteration of the tubule threshold for diacetic acid, as was suggested several years ago by Apple and Cooper.[7]

It is not at all clear why this phenomenon should occur in occasional cases. Often it is associated with oliguria, but oliguria is common in diabetic coma, and usually the concentration of diacetic acid in the urine is high. Dehydration and oliguria were more evident in Cases 1 and 2 than in these cases with negative ferric chloride.

[7] Apple, K. E., and Cooper, D. A., *Am. J. Med. Sc.*, 1927, **173**, 201.

Summary. A study has been made of the acetone bodies in blood and urine from a group of patients with diabetic ketosis, including 2 coma patients with urine giving a negative reaction with ferric chloride. The concentrations of free acetone in blood and urine were found to be similar in all cases; this observation supports the view that acetone is secreted into the urine by the physical processes of filtration and diffusion. The observed results were compatible with the suggestion that the cause of a negative urinary reaction with ferric chloride in certain cases of diabetic coma is due to a functional disturbance of the renal tubules, with elevation of the threshold for diacetic acid.

15475 P

Effect of Sulfathalidine and Sulfamethazine on Gaseous Distention in the Obstructed Small Intestine of Cats.

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It has been shown repeatedly that there are 3 sources of gas in intestinal distention (1) swallowed air, (2) decomposition of food, (3) diffusion, chiefly of nitrogen, from the blood into the intestines. According to Fine and his coworkers,[1] the nitrogen from the blood diffuses into the intestine in significant amounts only if other gases have collected in the gut in substantial volume. It has also been shown[1,2] that in the absence of food, swallowed air accounts for most of the gas present in the small intestine. The amount of swallowed air is variable within wide limits but can be controlled in great measure by withholding food and water and an inlying Levin tube. The fermentation or putrefaction of food is the second major source of gas in the obstructed small intestine. The coli-aerogenes-proteus group and certain clostridia, normally present in the small intestine, play a predominant role in this method of gas production. The inhibition of bacterial activity by antibacterial agents should contribute to a more complete control of meteorism. Hence a reduction in the number and metabolic activity of these groups of organisms might have a therapeutic effect.

Many of the sulfonamides now in use have a definite inhibiting action on enterobacteriaceae and clostridia, though each one to a different degree. Sulfathalidine (pthalylsulfathiazole) and sulfamethazine (dimethylsulfadiazine) clinically and experimentally have been shown to be effective against these

[1] Fine, J., and Levenson, W. S., *Am. J. Surg.*, New Series, 1933, **21**, 184.

[2] McIver, M. A., Benedict, E. B., and Cline, J. W., Jr., *Arch. Surg.*, 1926, **13**, 588.