in the adopted offspring after a few days (Table I). This demonstrates migration of these elements from the mother's skeleton to the offspring through the milk.

The immediate secretion of strontium in the milk was studied by injecting 0.1 cc radioactive strontium lactate solution intravenously into lactating mice; after 2 days, 19, 20 and 11.8% of the dose was recovered in the offspring. The immediate secretion of radioactive strontium in milk of 2 cows has also been studied.[3] During the 4 days following injection, 11 and 7.8% of the administered dose of radioactive strontium lactate (0.85 g of metallic strontium) was recovered in the milk.

In order to determine if the migration of the radioactive mineral salts from the mother's bones to the foetus and to the milk would alter the rate of excretion of radioactive strontium, the excreta of 6 mice previously injected with radioactive strontium were assayed for a period of one month. Three out of the 6 mice became pregnant. A slight increase (from 0.1-0.2% to 0.2-0.4% of the dose) in the daily rate of excretion of radioactive strontium occurred during the last 3 or 4 days of pregnancy, and particularly during the first 10 days of the lactation period.

Conclusion and Summary. Radioactive strontium and calcium have been used to study the mineral metabolism in mice during pregnancy. It appears that part of the calcium and strontium previously fixed in the skeleton of mice migrates to the foetus during the last days of pregnancy and to the offspring through the milk. When radioactive strontium lactate is injected intravenously into lactating mice and cows, appreciable amounts are excreted in the milk.

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Creatine-Creatinine Excretion in Neuromuscular Diseases Treated With Alpha-tocopherol and With Testosterone.*†

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Deficiency of vitamin E in guinea pigs and rabbits results in

[3] Erf, L. A., and Pecher, Charles, PROC. SOC. EXP. BIOL. AND MED., 1940, **45**, 762.

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† The alpha-tocopherol was kindly supplied by Merck & Co., Inc., Rahway, N. J.

dystrophy of the musculature which in some ways resembles muscular dystrophy in human beings. Mackenzie and McCollum[1] have shown that the nutritional muscular dystrophy of rabbits is readily cured by administration of alpha-tocopherol. These authors have studied the excretion of creatine and have found that increased creatinuria invariably attends the deficiency in rabbits and may precede the gross symptoms by 2 weeks or more. A marked reduction in urinary creatine occurs within 24 or 48 hours of vitamin E administration. The antidystrophy requirement of the rabbit for alpha-tocopherol does not exceed 1.0 mg per kilo per day. Verzar[2] has shown that rats develop creatinuria together with muscular dystrophy when put on a vitamin E-free diet. The creatinuria of these animals was suppressed by large doses of alpha-tocopherol. Fifty to 100 mg daily were necessary to reduce the creatine to normal values. When tocopherol therapy was discontinued creatine appeared again in the urine within 24 hours. Verzar believes that alpha-tocopherol is concerned with the fixation of the creatine in the body.

A number of workers have recently tried treatment with vitamin E in neuromuscular disorders in human beings. Bicknell[3] claims clinical improvement in 12 out of 13 cases of progressive muscular dystrophy, 2 cases with amyotrophic lateral sclerosis and one case of amyotonia congenita treated with wheat germ. Wechsler[4] reports clinical improvement in 2 early cases of amyotrophic lateral sclerosis in which synthetic alpha-tocopherol was employed. Stone[5] thinks that clinical improvement was obtained in 5 cases of progressive muscular dystrophy by adding wheat germ oil to the diet. Quite recently Shelden, Butt and Woltmann[6] reported negative results in 8 cases of progressive muscular dystrophy, 4 cases of progressive muscular atrophy, 6 cases of amyotrophic lateral sclerosis treated with alpha-tocopherol. All of these studies are based on clinical observations. Milhorat, Weber and Toscani[7] found that in 2 cases of dermatomyositis prolonged administration of 125 g of wheat germ daily was followed by decrease in creatinuria, increase in

[1] Mackenzie, C. G., and McCollum, E. V., *Science*, 1939, **89**, 370; *J. Nutrition*, 1940, **19**, 345.

[2] Verzar, F., *Schweiz. Med. Wochenschr.*, 1939, **69**, 738.

[3] Bicknell, F., *Lancet*, 1940, **1**, 10.

[4] Wechsler, I. S., *J. A. M. A.*, 1940, **114**, 948.

[5] Stone, S., *J. A. M. A.*, 1940, **114**, 2187.

[6] Shelden, C. H., Butt, H. R., and Woltmann, H. W., *Proc. Staff Meetings Mayo Clinic*, 1940, **15**, 577.

[7] Milhorat, A. T., Weber, F. C., and Toscani, V., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 470.

urinary creatinine and definite clinical improvement. As far as we are aware no biochemical studies have been reported on cases of progressive muscular dystrophy or amyotonia congenita treated with vitamin E.

Increased creatinuria has been found in many of the conditions in which there is atrophy of the musculature. It has been described in progressive muscular dystrophy, amyotonia congenita and amyotrophic lateral sclerosis. In these conditions the creatinuria is associated, as a rule, with a lowered ability to retain ingested creatine and with a subnormal output of creatinine. (Hunter,[8] Milhorat and Wolff.[9])

Report of Study. Treatment with alpha-tocopherol was tried in 2 cases of progressive muscular dystrophy and in one case of amyotonia congenita (Oppenheim's disease) in the Harriet Lane Home. In addition, the effect of testosterone on creatine-creatinine metabolism was studied in one case of amyotonia congenita and one case of muscular dystrophy; it has been shown that treatment with testosterone brings about a decrease of the amount of creatine excreted by castrate male rats (Kun and Peczenik[10]) and by human eunuchoids (Kenyon and coworkers[11]).

The patients were put on a diet low in creatine and 24-hour specimens of urine collected. In one patient (E.W.) there were nearly always losses in collecting the urine, so that in this case only the ratio of creatine to creatinine is significant, not the absolute amounts found in the urine. Creatine tolerance tests were made by giving 1.32 g of creatine by mouth in the morning and estimating the amount of this exogenous creatine excreted during the first 24 hours. The exogenous creatine not excreted within this time is considered retained and expressed in percent of the ingested amount. Creatine and creatinine were determined by the method of Folin.

The results are summarized on Table I. In no case was any clinical improvement observed as result of the treatment.

Conclusions. Neither alpha-tocopherol nor testosterone-propionate in the doses given had any effect on the creatine-creatinine excretion in the cases of amyotonia congenita and progressive muscular dystrophy studied. This should not be interpreted as failure of these substances as therapeutic agents. It indicates, however,

8 Hunter, A., *Creatine and Creatinine*, Longmans, Green and Co., Ltd., London, 1928.

9 Milhorat, A. T., and Wolff, H. G., *Ann. Int. Med.*, 1936, **9**, 834.

10 Kun, H., and Peczenik, O., *Pflugers Arch.*, 1935, **236**, 471.

11 Kenyon, A. T., Sandiford, I., Bryan, A. H., Knowlton, K., and Koch, F. C., *Endocrinol.*, 1938, **23**, 135.

TABLE I.

Avg daily excretion of			
Creatine mg	Total† Creatinine mg	Creatine in % of total %	Treatment
	L.M., ♂, 7 yrs, 30 kg, progressive muscular dystrophy.		
207	427	50	11 days without treatment.
196	372	54	6 " 100 mg alpha-tocopherol‡ daily parenterally.
198	453	44	5 days without treatment.
	J.W., ♂, 10 yrs, 22 kg, progressive muscular dystrophy.		
203	383	53	15 days without treatment.
208	373	56	19 " 110 mg alpha-tocopherol daily by mouth.‡
280	492	57	6 days without treatment.
242	414	58	8 " 220 mg alpha-tocopherol and 15 cc liver extract daily by mouth.
122+*	245+	50	14 days 25 mg testosterone-propionate twice weekly parenterally.
	E.W., ♀, 3½ yrs, 12 kg, amyotonia congenita.		
89+	120+	74	19 days without treatment.
78+	112+	70	20 " 200 mg alpha-tocopherol daily parenterally.‡
90+	127+	71	14 days without treatment.
	D.S., ♂, 6 yrs, 50 kg, amyotonia congenita.		
382	639	60	28 days without treatment.
354	572	62	14 " 50 mg testosterone-propionate twice weekly parenterally.
390	611	66	16 days without treatment.

*Losses in urine collection; only the creatine in % of total is significant.

†Creatine plus creatinine.

‡Alpha-tocopherol dissolved in olive oil when given by mouth and in peanut oil when given parenterally.

Creatine tolerance tests on patient L.M. showed 41% retention before treatment, 21% retention after treatment with alpha-tocopherol. The tests on patient J.W. showed 40% retention before treatment, 45% retention after the first 19 days of treatment with 110 mg alpha-tocopherol by mouth.

that alpha-tocopherol does not have the same inhibitory effect on creatinuria in neuro-muscular disturbances in human beings as in the nutritional muscular dystrophy in rabbits. This suggests a fundamental difference between nutritional muscular dystrophy in rabbits and progressive muscular dystrophy, amyotonia congenita and similar neuromuscular disturbances in human beings.