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A Biochemical Lesion of Lysine Deficiency in Man.*

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In a previous report[1] it was shown by nitrogen balance studies that lysine is a dietary essential for man. Observations on the urine were made at that time[2] in lysine-deficient subjects, but with the exception of an increased sulfate excretion no very definite changes were encountered. The present report describes further experiments which have confirmed our previous finding of a negative nitrogen balance and have extended our studies of the urinary constituents in this deficiency. These studies have revealed a striking rise in the non-ketone organic acids of the urine in this deficiency.

The lysine-deficient diets for the 3 subjects in the present study (No. 4 ♀, No. 5 ♂ and No. 6 ♂) were similar to those described in our previous report. The protein moiety was provided by an acid hydrolysate of deaminized casein, supplemented by 1.5% *l*-tryptophane and 1% *l*-cystine; this was fed in quantities of 0.1 g N/kg/day. The total caloric intake of the subjects varied from 2400-2700 cals./day. Since these subjects had been accustomed to a somewhat larger nitrogen intake we attempted to avoid the delay in reaching an initial nitrogen equilibrium by maintaining them on a protein-free diet for two days. This was followed by a 4-day control period in which nitrogen was supplied in the quantity mentioned above in the form of a lysine free amino acid mixture which had been supplemented by 6% *l* (+) lysine. It had been planned to submit the subjects to the lysine-deficient diet for a 24-day period; however, 5 days after this regimen had been instituted, all 3 subjects complained of nausea, dizziness and hypersensitivity to metallic sounds. No objective signs were, however, discovered by clinical examinations. A study of the curves in Fig. 1 reveals that a definite negative nitrogen balance had developed in all three subjects during this brief period.

Fig. 2 illustrates the sharp rise in non-ketone organic acids† in the urine which developed in all 3 subjects during this period. Because of the development of these symptoms and chemical findings, it was thought desirable to return to a lysine-containing diet. They were therefore placed upon a diet in which the nitrogen was supplied by a pancreatic digest of casein (Amigen) enriched by 1% *l*-cystine. Four days of this diet sufficed to relieve the subjective symptoms; nitrogen equilibrium was restored and organic acid excretion fell to the normal level.

The lysine-deficient diet was then resumed; after 4 days 2 of the 3 subjects complained as before. The organic acid excretion rose abruptly in all 3 subjects and negative nitrogen balance recurred in the 2 subjects in which measurements were completed. At this point subject No. 4 ♀ retired from the experiment. The 2 remaining subjects were then placed for a second time on the complete casein digest (Amigen) for 3 days. Once again the nitrogen balance became more positive. The organic acid excretion dropped and the symptoms of subject No. 6 ♂ were promptly relieved. Both subjects were then returned to the lysine-deficient diet for 13 days. In this period,

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1 Albanese, A. A., Holt, L. E., Jr., Brumback, J. E., Jr., Hayes, M., Kajdi, C., and Wangerin, D. M., PROC. SOC. EXP. BIOL. AND MED., 1941, **48**, 728.

2 Albanese, A. A., Kajdi, C., and Wangerin, D. M., *Fed. Proc.*, 1942, **1**, 97.

† This was determined by the method of Van Slyke and Palmer.[3] The absence of ketone bodies, which were tested for independently, permits the designation of "non-ketone" organic acids.

3 VanSlyke, D. D., and Palmer, W. W., *J. Biol. Chem.*, 1920, **41**, 567.

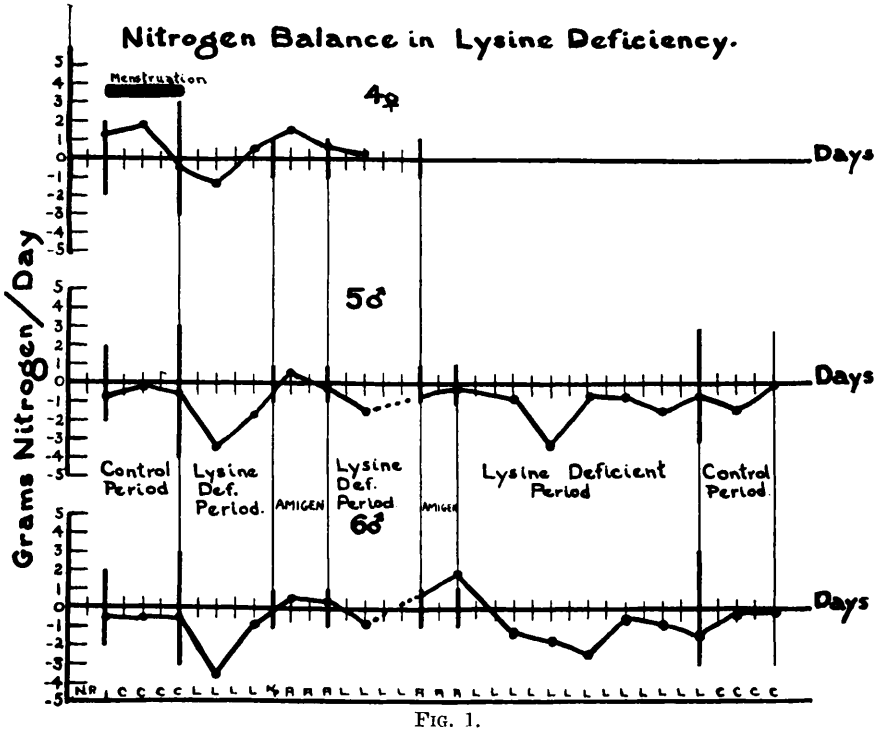
Nitrogen Balance in Lysine Deficiency.
Menstruation
4♀
5♂
6♂
Days
Grams Nitrogen/Day
Control Period
Lysine Def. Period.
AMIGEN
Lysine Def. Period
Lysine Deficient Period
Control Period

FIG. 1.

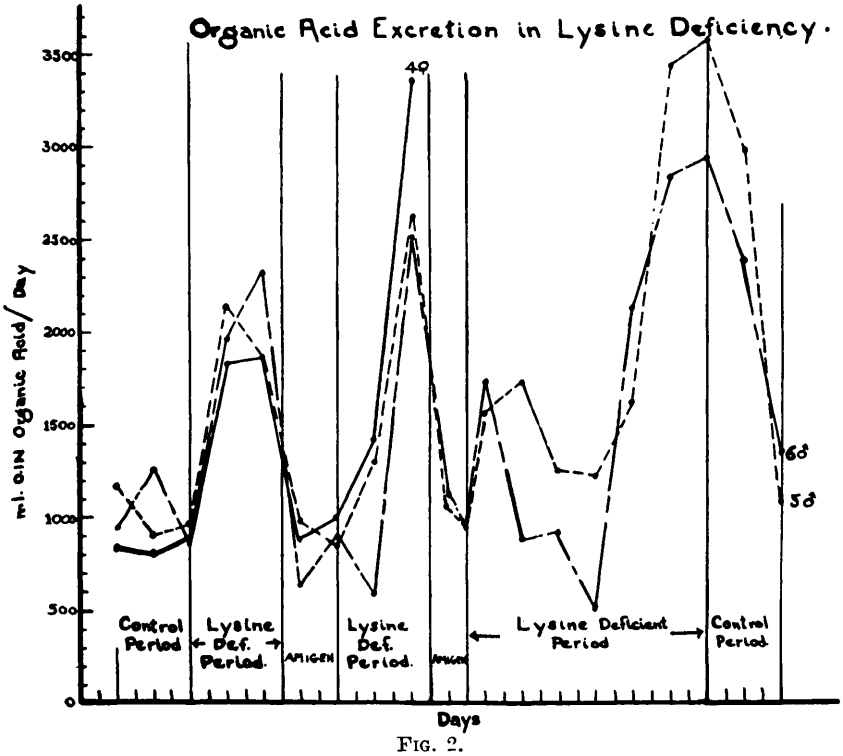
Organic Acid Excretion in Lysine Deficiency.
ml. 0.1N Organic Acid/Day
4♀
6♂
5♂
Control Period
Lysine Def. Period.
AMIGEN
Lysine Def. Period.
Lysine Deficient Period
Control Period
Days

FIG. 2.

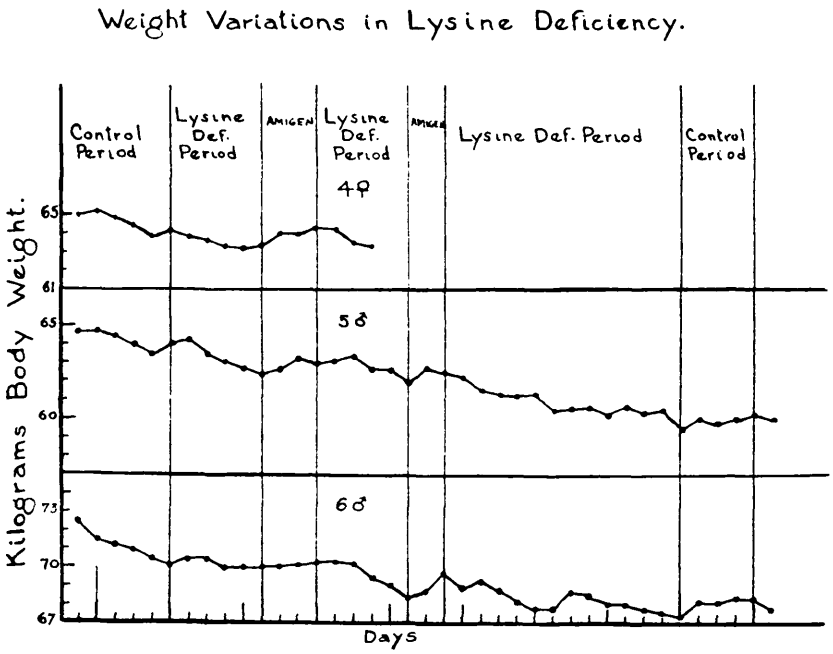

FIG. 3.

although a negative balance was immediately established and sustained, the organic acid excretion rise was delayed and none of the previous symptoms were reported. During the 4-day post-control period in which the lysine-deficient diet was supplemented with *l* (+) lysine, the negative nitrogen balance was restored and the organic acid output dropped to the normal level. The variations in weight of the subjects during the course of the experiment are shown in Fig. 3.

It would appear from these experiments that a high urinary excretion of organic acid is regularly induced by the lysine-deficient state in humans. The symptoms of nausea, dizziness and auditory hypersensitivity are apparently associated with this phenomenon. They are, however, much more conspicuous in some individuals than in others, for they were not observed in our previous studies of this deficiency.[1] It is regrettable that the organic acid output was not followed at that time.

The increased output of organic acids described above appears to be a biochemical lesion characteristic of lysine deficiency. We have not encountered it in parallel studies of deficiencies of other single amino acids—tryptophane, methionine and cystine, and it is clear from observations in the literature that a negative nitrogen balance does not *per se* give rise to this finding. It is, however, of interest to note that increases of non-ketone organic acids in the urine have been found in pneumonia,[4,5,6,7] nephrosis,[8] malnutrition,[9] postoperative acidosis,[10] premature infants[11] and in rickets of the Fanconi type.[12,13] A possible abnormality of lysine catabolism in these states is a matter upon which one can only speculate at the present time. The nature of the organic acid excreted by lysine-deficient subjects is now under investigation.

4 Palmer, W. W., *J. Exp. Med.*, 1917, **26**, 495.

5 Clausen, S. W., *Arch. Int. Med.*, 1925, **35**, 57.

6 Holten, C., *Ibid.*, 1926, **38**, 489.

7 Greenwald, I., *J. Biol. Chem.*, 1930, **85**, 447.

8 Perlzweig, W. A., personal communication.

9 Utheim, K., *Am. J. Dis. Child.*, 1921, **22**, 329.

10 Jeans, P. C., and Tallerman, K. H., *Am. J. Dis. Child.*, 1924, **28**, 253.

11 Branning, *J. Clin. Invest.*, 1942, **21**, 105.

12 Guild, H. G., Pierce, J. A., and Lilienthal, J. L., *Am. J. Dis. Child.*, 1937, **54**, 1186.

13 McCune, D. J., Mason, H. H., and Clarke, H. T., *Am. J. Dis. Child.*, 1943, **65**, 81.