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Endogenous Glycine Formation in Myopathies and Graves' Disease.

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The relation between glycine and creatin metabolism, first pointed out by Brand[1] and his associates, and extended by the therapeutic investigations of Milhorat, Thomas, and Techner,[2, 3] makes the question of the endogenous formation of glycine in disorders of creatin metabolism of considerable significance. In addition to the well recognized myopathies such as progressive muscular dystrophy and myasthenia gravis, abnormal excretion of creatin occurs in other diseases associated with muscular weakness, notably Graves' disease.

In a recent study[4] of the character of the creatin disturbance in progressive muscular dystrophy and Graves' disease, we found a rather striking similarity between the two disorders. In both there was (1) a diminished creatin tolerance, (2) an augmentation of the creatinuria following the ingestion of glycine, and (3) a similarity in the lesions produced in the skeletal musculature (from the pathological studies of Askanazy,[5] Naffziger,[6] and others).

We also studied[4] the rate of endogenous glycine formation as measured by hippuric acid excretion following the ingestion of sodium benzoate (method of Quick[7]), and found it to be unimpaired

[1] Brand, *Am. J. Physiol.*, 1929, **90**, 296.

[2] Milhorat, A. T., Thomas, K., and Techner, F., PROC. SOC. EXP. BIOL. AND MED., 1932, **29**, 607.

[3] Milhorat, A. T., Thomas, K., and Techner, F., *Deutsch. Arch. f. Klin. Med.*, 1933, **174**, 487.

[4] Proc. 25th annual meeting of Am. Soc. for Clin. Invest., May 8, 1933. *J. Clin. Invest.*, 1933, **12**, 966.

[5] Askanazy, *Deutsch. Arch. f. Klin. Med.*, 1898, **61**, 118.

[6] Naffziger, *Arch. Ophthalm.*, 1933, **9**, 1.

[7] Quick, *J. Biol. Chem.*, 1931, **92**, 65.

in both these diseases. Using the same method of investigation Freidberg and West[8] recently found that children with pseudo-hypertrophic muscular dystrophy were also able to form hippuric acid at the normal rate.

In the following paragraph are assembled the data from which our conclusions were drawn. They include normal controls and later studies of other myopathies. In addition to determining hippuric acid output, the excretion of glucuronic acid was also followed, since this substance might have been available for conjugation with benzoic acid in the case of a defect in glycine formation. Daily creatin and creatinine determinations were made with the subjects on creatin-creatinine-free diets in order to observe the effect of the stimulation of glycine formation and its subsequent diversion.

The hippuric acid excretion during the 4 hour period after the ingestion of 5.9 gm. of sodium benzoate, ranged from 4.3 to 6.4 gm. in 10 normal controls. Six patients, with Graves' disease and creatinuria, excreted between 3.7 and 6.0 gm. of hippuric acid during a similar period, with no significant differences after the abolition of the creatinuria by iodine. Repeated tests on 4 adults with progressive muscular dystrophy gave the following results: Case 1 (mild) 5.1, 5.6, 5.7 gm.; Case 2 (advanced) 4.2, 4.9, 4.3 gm.; Case 3 (advanced) 5.5, 5.5, 5.6 gm.; Case 4 (advanced) 4.4 gm. A miscellaneous group of myopathies gave these results: myotonia congenita, 5.8 gm.; myotonia atrophica, 4.9 gm.; periodic family paralysis (age 14) 3.7 gm. The only abnormally low result was obtained in a case of myasthenia gravis in which the excretion was 2.6 and 3.1 gm. on 2 tests.

Conclusions. Endogenous glycine formation following benzoate ingestion fell within normal limits in progressive muscular dystrophy, Graves' disease, and the other myopathies studied; except for one case of myasthenia gravis in which it was below normal, but possibly not significantly so. This does not exclude the possibility that the normal stimulus to glycine formation is inadequate in these diseases. There was no unusual excretion of glucuronic acid.

In several instances of progressive muscular dystrophy and Graves' disease, significant increases (70 to 310 mg.) in the excretion of creatin occurred on the day on which the benzoate was administered. This may have been due to the presence of increased amounts of glycine in the blood stream preliminary to its conjugation with benzoic acid, comparable to the effect of the in-

[8] Freidberg and West, *J. Biol. Chem.*, 1933, **101**, 449.

gestion of glycine. Or, what is more likely, it may have resulted from the loss of glycine through the urine, with an exacerbation of the defect in the creatin metabolism.

The normal synthesis of glycine in these patients and the ready formation of creatin when they ingest glycine, tend to place the defect in creatin metabolism beyond these stages. The inference is that the disturbance is located in the muscle itself, probably in the enzyme system which controls the breakdown and building up of phosphocreatin. The thyroid hormone is apparently involved in this process.

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The "Q" Deflection in Normal and Abnormal Human Electrocardiograms.

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Recent literature[1, 2, 3, 4] contains much work on the significance of the Q-wave, and, more particularly of a large Q-3. Attempts have been made in some of these studies[1, 4] to explain the mechanism underlying the production of a large Q-wave. Our knowledge of the mechanism of the normal Q-wave (*e. g.,* Lewis' and Wilson's theories) has been used as a basis for discussions of the abnormal Q-waves. Conclusions have been drawn by one author[4] from pathological correlations that the large Q-wave is representative of changes in a well localized portion of the heart (the left half of the septum posteriorly). Insufficient emphasis has been placed on the fact that the names Q, R and S are entirely arbitrary and that the Q-R-S system of terminology frequently gives the same name to parts of the electrocardiogram in the 3 standard leads that do not correspond in time, and different names to parts that do so correspond. We attempted an analysis of the Q-wave in normal records and in records of the large Q-3 type (described by Pardee[1])

[1] Pardee, H. E. B., *Arch. Int. Med.*, 1930, **46**, 470.
[2] Willius, F. A., *Am. Heart J.*, 1931, **6**, 723.
[3] Carr, F. B., Hamilton, B. E., and Palmer, R. S., *Am. Heart J.*, 1933, **8**, 519.
[4] Fenichel, N. M., and Kugell, V. H., *Am. Heart J.*, 1931, **7**, 235.