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Significance of Creatine in Progressive Muscular Dystrophy, and Treatment of this Disease with Glycin.

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Ever since Duchenne (de Boulogne)[1] made his classical studies of the progressive muscular atrophies the pathogenesis has been a subject of much contention. The view held by Duchenne[1] that the disease is primary in the muscles is supported by the clinical and pathological findings of many able workers,[2,3] but despite this, practically all methods of treatment have been based on the theory that the condition is secondary to some disturbance in the innervation.[4,5]

Patients with this disease show a creatinuria even when maintained on a creatine-free diet, and in contradistinction to the normal subject excrete ingested creatine almost quantitatively (65-100%). This inability to retain ingested creatine is in proportion to the severity to the disease.

In our investigations on the origin of creatine,[6] many substances that could be considered biologically related to creatine were studied. We were able to confirm the findings of Gibson and Martin[7] who administered gelatin, and of Brand, Harris, Sandberg, and Ringer[8] who were the first to recognize the relationship of glycin, that the ingestion of this amino acid in these cases is followed by a large increase in the creatinuria. This significant relationship between glycin, a substance which the normal subject can readily synthesize,

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1 Duchenne, G. B. (de Boulogne), *De l'electrisation localisee*, 2nd Ed., Paris, 1861.

2 Erb, W., *Arch. f. klin. Med.*, 1884, **34**, 467; *Zeitschr. f. Nervenheilkunde*, 1890, **1**, 1.

3 Friedreich, N., *Ueber progressive Muskelatrophie*, Berlin, 1873.

4 Kuré Ken, *Die vierfache Muskelinnervation einschliesslich der Pathogonese und Therapie der progressiven Muskeldystrophie*, Urban u. Schwarzenberg, Berlin, 1931.

5 G. de N. Hough Tr., *J. Bone and Joint Surg.*, 1931, **13**, 669.

6 To appear shortly in Hoppe-Seyler *Z. f. physiol. Chem.*

7 Gibson, P. B., and Martin, F. T., *J. Biol. Chem.*, 1921, **49**, 319.

8 Brand, E., Harris, M. M., Sandberg, M., and Ringer, A. I., *Am. J. Physiol.*, 1929, **90**, 296. Brand, E., Harris, M. M., Sandberg, M., and Lasker, M., *J. Biol. Chem.*, 1930, **87**, lix. Brand, E., Harris, M. M., *J. Biol. Chem.*, 1931, **92**, Proc. l ix.

and creatine, which has been demonstrated to play an important rôle in muscle function, suggested that the prolonged administration of this amino acid might have an influence on the clinical and chemical course of this disease. We have studied 6 patients during 8 experimental periods each of a few months' duration. Three of these patients had the clinical picture known as progressive muscular dystrophy, and 3 the symptom complex designated as pseudohypertrophic muscular atrophy. The daily ingestion of 5 gm. of glycin was followed by a definite rise in the creatinuria; 15-20 gm. increased the daily excretion of creatine 300-500 mg., the more advanced cases excreting the larger amounts. The percentage increase naturally depends upon the height of the control level. In one case the increase was 100% (500 mg.); in others where the previous creatinuria level was low the smaller increase (300 mg.) represented a percentage increase of 1000%.

After a period of some weeks (depending on how advanced the case is) the creatinuria begins to decrease despite the continuance of glycin until it falls to the former control level. In some cases this requires only 2 to 3 weeks; in one advanced case even after 8 weeks the previous level had not been reached. In one patient the creatinuria fell to a value below that observed before glycin was given. Coincident with the decrease in the creatinuria there is a rise in the creatinine output, and an improvement in the patient's ability to hold ingested creatine. These changes in the metabolism disappear in the course of a few weeks after the cessation of glycin ingestion, and return if the administration is again instituted.

While these changes in the metabolism are taking place, the condition of the patient improves in a remarkable manner. The first symptom manifested in half of our patients was a curious feeling in the muscles which they describe as a "crawling, rumbling" sensation, which in one case was so severe that sleep was definitely interfered with. In these patients muscle groups affected were those whose function was most impaired. One patient who was given glycin during 2 periods 6 months apart experienced the sensation in the same muscle groups both times. This curious feeling makes its appearance some days before the creatinuria begins to fall, and disappears after further administration of glycin in 3 to 14 days. One patient had such muscle sensations on admission, but after glycin administration they completely disappeared for the first time in over a year, and did not return.

The next change in the clinical course is the disappearance of the fatigue that frequently constitutes a prominent and distressing symp-

tom in this disease. The muscles that had previously felt tired and heavy now feel refreshed and lighter, and the patients often desire to make muscular movements they have not been able to make for a long time. Gradually the function of certain muscle groups so improves that activities can be performed that had been impossible for years (stair climbing, arising from the floor unaided, bicycle riding). The degree of improvement differs not only in different patients, but in different muscles of the same patient. The time required for such improvement varies widely. One patient showed a remarkable improvement in 3 weeks; in another no definite increase in muscle function could be demonstrated at the end of 9 weeks, although there was much subjective improvement.

Two patients who showed considerable improvement after glycin administration were permitted to interrupt the treatment for 3 months. The improvement continued for another 3 to 4 weeks, and then gradually disappeared until their condition returned to its previous status. The changes in the metabolism corresponded to these changes in the clinical condition. One of these patients has again been given glycin, and after 3 weeks shows the same remarkable improvement in the same muscle groups as before.

Besides these cases we have studied, as controls, 3 patients with extensive muscular atrophy due to other causes (amyotrophic lateral sclerosis, severe chronic rheumatism of the joints, congenital idiocy). These patients also showed a creatinuria on a creatine-free diet, and could retain only about 50% of ingested creatine. The administration of glycin was followed by no increase in the creatinuria. It is suggested that after further studies of this kind the reaction to glycin might be of value in the differential diagnosis of the muscular atrophies. During 5 weeks of glycin administration (15 gm. daily) the patients felt in no way improved, and had none of the symptoms experienced by our other patients. At the end of the period no change in the metabolism could be demonstrated, and the inability to retain ingested creatine had not improved.

These findings, in our opinion, indicate that the improvement obtained in our cases of progressive muscular dystrophy and pseudohypertrophic muscular atrophy is not due to any temporary irritative action of this amino acid, but that glycin has an important function in muscle physiology, and a significant rôle in the pathogenesis and treatment of this disease.