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Effect of Testosterone Propionate and Methyl Testosterone on Creatinuria in Progressive Muscular Dystrophy.

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Progressive muscular dystrophy is a disease in which large groups of voluntary muscles undergo primary degeneration and atrophy. The disease is hereditary and familial, although isolated cases are encountered. Atrophy is marked in all forms, but hypertrophy or pseudohypertrophy is an early and prominent symptom in one form. Numerous attempts have been made to understand the nature of the process underlying this disorder, to the end that effective treatment may be found. Failure thus far to evolve a basis for therapy has characterized most of the results of studies on this disease, although enthusiastic claims have been advanced from time to time only to have been discarded at the hands of sober and objective therapeutists.

During a period of 2 years, in which we have had 40 cases of progressive muscular dystrophy under study, we have been impressed, as have other workers, with the marked predilection of this disease for males, in whom the disease, if established early, tends to run a much more acute course than in the occasional female in whom the disease is encountered. This observation, together with the fact that the disease in the male tends to become less acute following the onset of puberty, leads one to the hypothesis that the essential aberration in progressive muscular dystrophy is one connected closely with the biological phenomenon of maleness on the one hand and, perhaps, with those systems concerned with growth and development on the other. Since certain of these phenomena are mediated through the hormones of the anterior pituitary, the adrenal cortex, and the gonads, it was believed that an investigation of the effects of these agents on the metabolism and clinical course of patients with this disease should be carried out, in so far as modern technics of endocrinology permit.

A number of reports have appeared recently concerning the effects of the steroid hormones, particularly testosterone, on the growth and development of the muscular system, and more specifically on the metabolism of creatine.[1-5] On the whole, however, reports have been equivocal, and in some instances flatly contradictory. Creatinuria has long been regarded as the most consistent abnormality in the metabolism of patients with progressive muscular dystrophy. Any agent, therefore, which affects the excretion of creatine, should be of interest in a study of this syndrome. Accordingly, a study of the effects of a number of the available members of the steroid hormone series on the metabolism of creatine, creatinine, and glycocyamine, in normal subjects and in patients with progressive muscular dystrophy, was begun. Five children between the ages of 7 and 12 years, in whom progressive muscular dystrophy was moderately advanced, were chosen for study. Since a somewhat variable physiological creatinuria is encountered in the pre-adolescent male, 4 normal children of comparable ages were selected as control subjects. Control subjects and patients with muscular dystrophy were placed on diets of constant composition and base line values were obtained for the excretion of creatine, creatinine and glycocyamine.

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4 Duckworth, D. A., *J. Clin. Endoc.*, 1942, **2**, 13.

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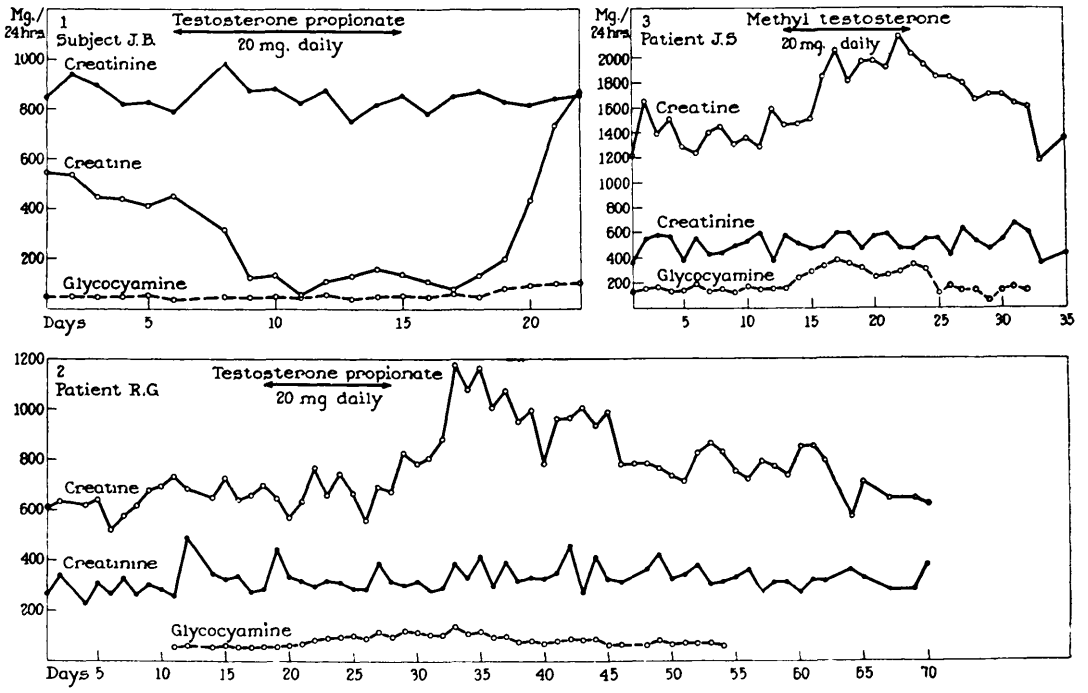

FIG. 1.

The excretion of creatine, creatinine, and glycocyamine in the urine of normal subjects and patients with progressive muscular dystrophy following the administration of testosterone propionate and methyl testosterone.

The determination of glycocyamine was included in these studies because of its known role as an intermediary substance in the biological synthesis of creatine from glycine, arginine, and methionine,[6,7] and because its excretion is known to be altered in patients with muscular dystrophy.[8] After a control period during which the excretion of these substances was found to be constant from day to day, testosterone propionate† was administered intramuscularly to normal subjects and patients, in doses of 20 mg a day, over a period of 10 to 14 days. The hormone was then discontinued and determinations of creatine, creatinine, and glycocyamine were continued until approximately the former levels of excretion of these substances were reached.

Certain differences in the effect of testosterone on the excretion of creatine and glycocyamine in normal subjects and in patients exhibiting muscular dystrophy were immediately apparent. There was a marked drop in the excretion of creatine in each of the normal controls within 72 hours after the administration of testosterone propionate which persisted as long as the hormone was continued. Immediately upon withdrawal of the hormone, however, there was a marked creatinuria which was maintained for several days. Results on a typical normal subject are given in Fig. 1 (No. 1, Subject J.B.). In the patients exhibiting dystrophy (No. 2, Patient R.G.), on the other hand, there was no significant change in the output of creatine during the interval in which the hormone was administered. However, as in the normal subjects, following withdrawal of testosterone, a marked increase in the excretion of creatine

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8 Gilder, H., Shank, R. E., and Hoagland, C. L., unpublished data.

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and glycocyamine was observed, which lasted for a period of several days, after which there was a slow decrease to the former base line values. No significant change in creatinine excretion was apparent.

In contradistinction to testosterone, methyl testosterone has been shown to produce creatinuria in normal subjects.[9] However, creatine storage is said to occur with this agent,[10] and the accompanying creatinuria has been explained as being due to an accelerated synthesis of creatine.[9] Accordingly, 2 patients with progressive muscular dystrophy were given 20 mg of methyl testosterone† orally for a period of 10 days, and analysis of the urine for creatine, creatinine, and glycocyamine was performed as before. The results obtained with a typical patient are given in Fig. 1 (No. 3, Patient J.S.). In contradistinction to the effects observed with testosterone there was a marked increase in creatine excretion as soon as the administration of methyl testosterone was begun, and the increase was maintained as long as the hormone was continued. A marked increase in urinary glycocyamine likewise occurred. Upon withdrawal of the hormone, however, no further increase occurred in the output of creatine or glycocyamine. Indeed, there was a rapid drop in the excretion of both creatine and glycocyamine until the previous levels of output were approximated.

One possible explanation for the marked output of creatine occurring in patients with progressive muscular dystrophy, following the withdrawal of testosterone, is that creatine storage had occurred as a result of the administration of the hormone in spite of the fact that no marked changes in creatine excretion were demonstrated while the hormone was being administered. In other words, although creatine was retained during the period of hormone administration, the storage was not sufficient to be reflected in significant changes in a high creatine output over the relatively short periods covered by the analyses. In a later patient, in whom the disease was in its earliest stages, and the creatinuria only slightly above normal, a definite decrease in creatine output *was* observed soon after the administration of the hormone was begun.

The administration of testosterone has been claimed to produce an increase in the deposition of creatine in the muscles of normal animals, as revealed by direct measurement of the concentration of creatine in the muscle,[10] and by a marked retention of creatine as reflected in a drop in its excretion in the urine.[3,10,11] No reports have been found, however, of studies on the creatine output of patients with progressive muscular dystrophy following the giving of this hormone. If creatine retention, which occurred as a result of the testosterone medication, may be regarded as a true storage phenomenon, it would indicate that in progressive muscular dystrophy the capacity to store creatine is not irreversibly altered. Moreover, it would justify the administration of the hormone in therapeutic amounts over a prolonged interval of time in order to learn if muscle function can be improved thereby. Studies directed toward this end are underway and the results will be reported in a subsequent communication.

[9] Samuels, L. T., Henschel, A. F., and Keys, A., *J. Clin. Endoc.*, 1942, **2**, 649.

[10] Pizzolato, P., and Beard, H. H., *Endocrinology*, 1939, **24**, 358.

[11] Williamson, M., and Gulick, A., *Endocrinology*, 1941, **28**, 654.