Influence of Nitrogen Intake on Nitrogen-Retaining Action of Testosterone Propionate. (20454)

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With the discovery(1) that androgens induce nitrogen retention in the castrate dog, much effort has been expended in elucidating the nature of the response and the factors regulating it. Our interest in the problem was stimulated by the fact that only fragmentary information was available regarding the influence of nutritional status and, particularly, nitrogen plane on the degree of response to testosterone. Kochakian and Van Der Mark (2) have recently confirmed and extended their earlier findings that "once an adequate protein intake is provided a further increase in the protein (intake) of the rat . . . does not enhance the overall protein anabolic activity of testosterone." Earlier, Albright and his associates(3) expressed the view that the absolute influence of androgen on urinary nitrogen should diminish as the protein consumption declines, and Kenyon and Knowlton(4) had indeed demonstrated such a tendency in a study on the normal, human adult.

It appeared important, therefore, to determine the response when the level of nitrogen intake was reduced to the minimal maintenance requirement. At this low level of nitrogen intake, it should also be possible to determine whether or not testosterone functions by "facilitating", *i.e.*, making more efficient, the utilization of nitrogen, an hypothesis that we have considered as one possible explanation of the mechanism of action.

Methods. The 2 dogs used were pedigreed, adult, male beagles that had been castrated approximately one year prior to use in this study. Each dog was housed in an individual metabolism cage throughout the entire investigation. The animals were fed daily at the same time; the composition of the iso-caloric, high nitrogen and low nitrogen diets are given in Table I. The nitrogen contents of the diets were determined at frequent intervals by Kjeldahl analyses. Urines were collected under toluene and the nitrogen content determined daily using a micro-Kjeldahl distillation procedure. Fecal nitrogen was not done routinely but was determined at frequent times during the course of the study. The results were sufficiently close to 10% of the dietary intake to justify the use of this figure for computing the fecal N contribution to the daily total N excretion. The average N excretion (urine plus calculated fecal) for 3 consecutive days constituted one collection period. Testosterone propionate (25 mg/ml in sesame oil) was injected, intramuscularly, for the periods indicated in Fig. 1. The low nitrogen diet (0.20 g N/kg b.wt.) was selected experimentally and was at a level for Dog VII, which would just maintain this animal in nitrogen equilibrium. Below this intake positive nitrogen could not be obtained. For Dog V, this N-level produced a slightly negative balance.

TABLE I. Composition of Diets* (g %).

	A	B
Casein	23.5	11.8
Sucrose	53.0	65.0
Lard	18.5	18.2
Wesson's salts	2.0	2.0
Agar	3.0	3.0
Cal/kg b.wt provided	70	70
g N/kg b.wt provided	0.45	0.2

* Each animal received one high potency multivitamin capsule per day.

Results and discussion. The results of these experiments are presented in Fig. 1. It will be noted that both animals exhibited a significant nitrogen retention following the first administration (interval II) of testosterone propionate. The response persisted into the post-injection interval (interval III) which is in confirmation of the observations of Thorn and Engel(5). It is of interest that no significant nitrogen "rebound" was observed in any of the trials. When the animals were again subjected to testosterone propionate treatment (interval V), Dog VII exhibited a clear-cut nitrogen retention but the response of Dog V was not manifested until the

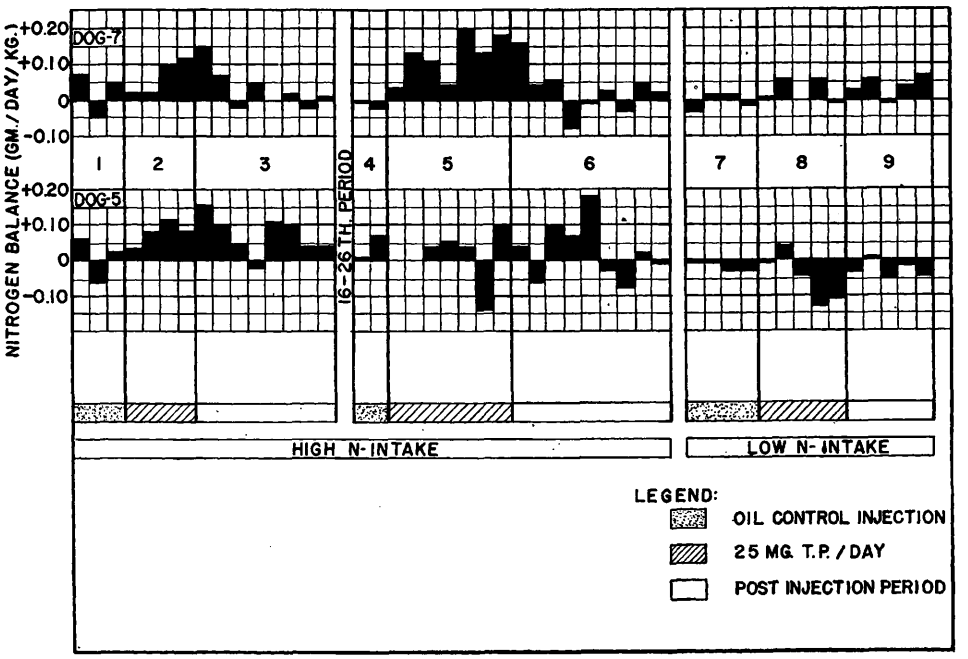

FIG. 1. Nitrogen retaining activity of testosterone propionate at two different levels of nitrogen intake in castrate dogs.

post-injection interval (interval VI).

The animals were next equilibrated on a low nitrogen intake (0.20 g N/kg/day) and when stabilized on the diet, testosterone propionate treatment was begun (interval VIII). No significant nitrogen retention occurred. In fact, it would appear that in Dog V, a more negative balance was obtained. The significance of this response is not clear but in certain experiments (unpublished) in this laboratory with rats on a minimal nitrogen intake, the occurrence of a strongly-negative nitrogen balance during treatment with testosterone propionate was also observed.

These data clearly demonstrate that in the region of the minimal, nitrogen-maintenance requirement, the nitrogen-retaining activity of testosterone propionate is absent. These results also make it improbable that testosterone acts by "facilitating" the utilization of dietary nitrogen. That the data presented may have certain clinical or therapeutic implications would appear obvious particularly when it is realized that individuals with very low nitrogen intakes may be in perfect balance. Hence, the mere presence of nitrogen equilibrium is not adequate in itself to assure a response to testosterone. A knowledge of the protein or other stores may be of more importance in determining whether or not a nitrogen retention can result from testosterone treatment.

Summary. The nitrogen-retaining activity of testosterone propionate in the castrate, male dog is manifested when the animal is maintained at levels above the minimal-maintenance nitrogen level of intake. At the minimal level of nitrogen, no nitrogen retention could be induced.

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