CLINICAL EXPERIENCES WITH A NEW ANABOLIC STEROID, 19-NORTESTOSTERONE FURYLPROPIONATE IN THE TREATMENT OF IMMATURE AND MATURE BABIES

BY

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ABSTRACT

19-nortestosterone furylpropionate (Demelon), a newly synthetized anabolic steroid in Japan, showing an excellent anabolic effect on m. levator ani of the rat, was given by subcutaneous injection to 51 newborn babies weighing over 2501 g and to 26 immature babies, and the increase in body weight and the days required for the recovery of weight at birth were observed under consideration of the lactation and other factors.

INTRODUCTION

It has been a widely recognized fact that testosterone has protein anabolic action since Kochakian et al. reported in 1936 that the extract from male urine precipitated the accumulation of nitrogen in the body, interpreting it to be the result of the acceleration of protein anabolism in the body.

However, the prolonged clinical use of testosterone for the purpose of accelerating protein anabolism tends to produce intense masculinization by its inherent property, so that there have been great obstacles against the use of the drug for women and infants. In order to overcome such obstacles, a variety of studies have been carried out in search of a substance which presents weak masculinization and strong anabolism.

In 1941 Eisenberg and Gordan observed the phenomenon that the perineal muscular group of castrated male rats was especially sensitive to the anabolic steroid, and recognized that protein anabolism could be represented by the increase in weight of the levator ani muscle. The levator ani muscle test has, since then, been a powerful means for screening protein anabolic steroids and led to discovery of many excellent anabolic steroids now in prevalent use.

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19-nortestosterone is known to have lower masculinizing factor, and yet its anabolic action is almost as strong as that of testosterone. It is also known that only the factor of protein anabolism can be intensified by changing its 17th hydroxyl group.

19-nortestosterone furylpropionate (Demelon) is a compound newly synthetized in Japan (Mochida Pharmaceutical Co., Ltd.), showing an excellent effect of protein anabolism under the levator ani muscle test. It was subjected to clinical trials on immature and mature babies. The following are the results of clinical experiments.

I. Subjects of Experiment and Method of Administration

1) Effect of Demelon on Mature Babies:

51 newborn babies weighing over 2501 g at the time of delivery were selected at random, and 10 mg of Demelon was given by hypodermic injection to them on the 1st day following birth. Then, the change of the body weight and amount of milk were observed until the 11th or 16th day after birth.

The control group consisting of 445 newborn babies weighing over 2501 g at birth, who were delivered approximately on the same year and month, were kept under observation so that the change of body weight and the amount of milk could be comparatively followed up.

2) Effect of Demelon on Immature Babies:

26 newborn babies weighing less than 2500 g at the time of delivery were selected at random, and a dose of 10 mg of Demelon was administered to them by hypodermic injection on the 1st, 7th, and 14th days after birth. Then the change of their body weight and amount of milk were observed until the 22nd–30th day after birth.

For the control, 78 newborn babies weighing less than 2500 g at birth and born in approximately the same year and month, to whom no hormone had been administered, were selected at random for the purpose of comparison. Reference was made to the weight curves of immature babies supplied by Dancis, O'Connell & Holt in 1948.

II. Numerical Expressions

Both the experimental group and the control group were divided by the difference in body weight in such a manner as the following subgroups might be formed: 1501–1750 g, 1751–2000 g, 2001–2250 g, ..., 3001–3250 g, and 3251–3500 g, with a difference of 250 g between one another.

The weight was expressed in percentages compared with the weight

at birth (100) of each case. And the average weight of each subgroup was figured out. The rates of decrease and increase in weight were also expressed in percentages.

The amount of milk was represented by the value (g) of actual measurement. In other words, in case of suckling babies the difference in their body weight between before and after milk feeding was considered as the amount of milk for one feeding, and the daily total was obtained. In case of bottle-fed babies, the amount was derived directly from the graduations of the bottle.

In order to obtain the number of days required for the babies to regain the weight at birth, the calculation was based on the curves of average body weight percentages for each subgroup, not through obtaining the average number of days for each case.

III. Judgement of Test Results

The test results were judged in the light of the following points. As described above, the subject groups were divided into subgroups with different weight ranges for the reason that the variation of body weight and lactation depends upon the weight at the time of delivery.

The variation of weight in newborn babies can be expressed by a standard curve if a lot of cases are studied. However, no one would deny the fact that the variation covered considerably wide ranges. Therefore, when the effect of the administration of the anabolic steroid on body weight is evaluated, it often happens that the effect may be interpreted in many ways if the formation of the control curve is inadequate.

For prevention of such error, the judgement of effect was based on the comparison made in each case with the standard weight curve, for example, the curve of Dancis and Holt for immature babies.

In the present experiment, it was aimed to do a comparative study of the wide range of variation in the body weight and amount of milk in newborn babies. Therefore, the average body weight and the amount of milk were figured out for all the cases under test, comparing the results with the control group considered to have been placed under the same conditions because of their birth in approximately the same year and month.

Furthermore, since it was possible to cause erroneous judgement of the results if the mean values were allowed to fluctuate largely by including the maximum and minimum values which were extremely far away from the average value, the cases were excluded showing such extreme values in the both experimental and control groups.

IV. Classification of Body Weight at Birth for Each Subgroup

The number of cases and the average body weight (g) at the time of delivery in the subgroups classified by weight of the experimental and control groups are shown in the following table (Table 1).

Table 1. Classification of Body Weight at Birth

Weight at Birth (g) for Each Subgroup	Demelon Group		Control Group	
	Number of Cases	Average Weight at Birth (g)	Number of Cases	Average Weight at Birth (g)
4251—4500			3	4375.0
4001—4250			12	4077.5
3751—4000			17	3838.5
3501—3750	8	3673.8	69	3619.9
3251—3500	8	3386.3	100	3367.0
3001—3250	11	3121.8	102	3121.5
2751—3000	11	2865.9	90	2905.5
2501—2750	13	2652.7	52	2643.8
2251—2500	13	2361.2	45	2408.0
2001—2250	6	2168.3	16	2129.7
1751—2000	5	1924.0	2	1830.0
1501—1750	2	1670.0		

V. Test Results

1) Effect of Demelon on the Rate of Physiological Decrease in Weight:

The following table shows the rate of physiological decrease in weight of each subgroup (Table 2).

In general, no striking difference seemed to be discerned between the experimental group and the control group. Looking into the details, it was found out that a significant difference existed between the groups in 4 subgroups of 2751–3250 g, 2251–2500 g, and 1751–2000 g. In other words, in the three subgroups over 2251 g the rate of decrease was higher in the Demelon group, while in the subgroup of 1751–2000 g the rate was higher in the control group.

However, the physiological decrease in body weight was generally most conspicuous in a couple of days after birth, so that even if Demelon is administered to the baby on the first day after birth, its effect would not be likely to manifest during the period of the natural decrease in body weight. Accordingly, the variation described above might be best explained as the

Table 2. Effect of Demelon on the Rate of Physiological Decrease in Weight

	Demelon Group	Control Group
Weight at Birth (g) for Each Subgroup	Rate of Physi. Dec. in Weight	Rate of Physi. Dec. in Weight
4251—4500		5.0
4001—4250		4.9
3751—4000		3.7
3501—3750	2.7	3.0
3251—3500	3.2	3.4
3001—3250	3.8	3.1
2751—3000	4.6	3.9
2501—2750	3.7	3.5
2251—2500	6.0	3.9
2001—2250	6.3	6.1
1751—2000	6.6	8.4
1501—1750	11.0	

result of the irregular rate of decrease in individual cases belonging to each subgroup.

Generally speaking, the rate was rather uniform in the subgroup of 2501–4000 g, but the rate increased abruptly in subgroups less than 2000 g. On the other hand, the rate was rather high for large babies weighing over 4000 g.

2) Effect of Demelon on the Number of Days Required for Recovery of Body Weight at Birth:

The comparison made between the experimental group and the control group on the number of days required for the babies to regain their weight at birth in reference to the average weight curves, is shown in the following table.

Generally the number of days for restoring the weight at birth is obviously smaller in the Demelon group than in the control group. However, there was no difference at all between the groups for two subgroups of 2501–3000 g. In the subgroup of 2251–2500 g, the number was larger in the Demelon group. In consideration of the fact that the rate of physiological decrease in weight was higher in the Demelon group for the 2751–3000 g subgroup, the equal number of days for both groups to regain the weight at birth indicated that the increase and recovery of weight was more remarkable in the Demelon group. It is considered that for the subgroup of 2251–2500 g the higher rate of decrease in weight of the Demelon group must have influenced the number of days for regaining the weight at birth.

The general tendency was that the number of days for regaining the

weight at birth was augmented in the babies weighing less than 2000 g or over 3501 g (Table 3).

Table 3. Average Number of Days for Recovery of Born Weight

	Demelon Group	Control Group
Weight at Birth (g) for Each Subgroup	Average Number Days for Recovery of Born Weight	Average Number Days for Recovery of Born Weight
4251—4500		
4001—4250		12
3751—4000		12
3501—3750	9	11
3251—3500	4	8
3001—3250	5	7
2751—3000	6	6
2501—2750	5	5
2251—2500	9	6
2001—2250	7	8
1751—2000	10	12
1501—1750	13	

3) Effect of Demelon on the Rate of Increase in Weight:

Starting from the day when the weight of a baby was reduced most, the increase in body weight during a definite period of time was calculated in percentages, with the results shown in the following table. The increase rate was expressed by the daily average (%) of weight increase for 7, 11, 14, 21, and 28 days starting on the day when the lowest weight value was found. For instance, the numerical value of 0.9 for 7 days means that the daily increase in weight was 0.9% of the weight at birth for the period of 7 days starting on the day when the lowest weight was obtained (Table 4).

Through the periods of observation, we found out that the rate of increase in weight was generally remarkable during the administration of Demelon. Demelon was given to babies weighing over 2501 g only once. And if their rate of increase in weight was compared with that of the control group, it was known that the weight increases at a comparatively high rate for 7 days during the administration of Demelon, and that the condition tended to be continued. The rate of increase in weight for babies weighing less than 2500 g during the administration of Demelon, especially on the 21st and 28th days, was found to continue for about two weeks, if Demelon was administered repeatedly. For the final injection was made on the 14th day after birth.

Table 4. Rate of Increase in Weight (%)

Weight at Birth (g) for Each Subgroup	Demelon Group					Control Group				
	Days of Observation									
	7	11	14	21	28	7	11	14	21	28
4001—4250						0.24	0.5			
3751—4000						0.23	0.27			
3501—3750	0.48	0.46				0.35	0.36			
3251—3500	0.93	1.29				0.53	0.58			
3001—3250	1.06	0.77				0.55	0.66			
2751—3000	1.2	1.1				0.76	0.76			
2501—2750	0.85		1.44			0.80		0.79		
2251—2500	1.02		1.34	1.63	1.65	0.76		1.0	1.08	1.23
2001—2250	1.3		1.31	2.03		1.06		0.98	1.28	1.53
1751—2000	0.76		1.04	1.2	1.63	1.1		0.95	1.53	2.06
1501—1750	0.96		1.01	1.2	1.43					

As for the subgroup of 1751–2000 g, the rate was remarkable on the 21st and 28th days in the control group, because the number of cases was small and it happened that the cases with much increases in weight were included in our calculation.

4) Effect of Demelon on the Amount of Milk:

The following graphs show the amount of milk in the experimental and control groups on the 7th, 11th, 14th, 21st, and 28th days after birth. The amount was expressed by the average measured value (g).

It was recognized that the amount of milk was generally increased in the Demelon group. In other words, body weight increased somewhat correlatedly with the amount of lactation on account of the administration of Demelon (Table 5).

The increase in body weight was specially remarkable in the control group weighing 1751–2000 g, and it was also evident that the amount of milk increased, as if proving a certain correlation existing between the two factors.

In the formation of the curves of the amount of milk throughout all the periods, there was such a wide day-to-day variation that the unit of the axis had to be too large to give a clear-cut difference between the experimental group and the control group.

The readers are requested to refer to the curves of body weight and the curves of amount of milk of three subgroups weighing respectively 1751–2000 g, 2251–2500 g, and 3251–3500 g in Tables 1, 2, and 3. As for the subgroup of 1751–2000 g, since the control group was not considered to be

Table 5. Amount of Milk (g)

Weight at Birth (g) for Each Subgroup	Demelon Group					Control Group				
	Days after Birth									
	7	11	14	21	28	7	11	14	21	28
4001—4250						596.7	610.0			
3751—4000						580.8	750.0			
3501—3750	592.0	662.5				578.6	618.2			
3251—3500	579.2	725.0				547.3	602.8			
3001—3250	515.2	560.0				535.7	575.7			
2751—3000	510.0	605.0				498.8	584.0			
2501—2750	436.2		545.0			463.2		511.1		
2251—2500	360.8		511.7	600.0	735.0	411.4		495.2	586.2	641.4
2001—2250	385.0		518.3	713.8		332.0		428.8	545.4	585.0
1751—2000	260.6		355.2	461.3	516.7	215.0		295.0	522.5	597.5
1501—1750	175.0		211.5	273.5	396.0					

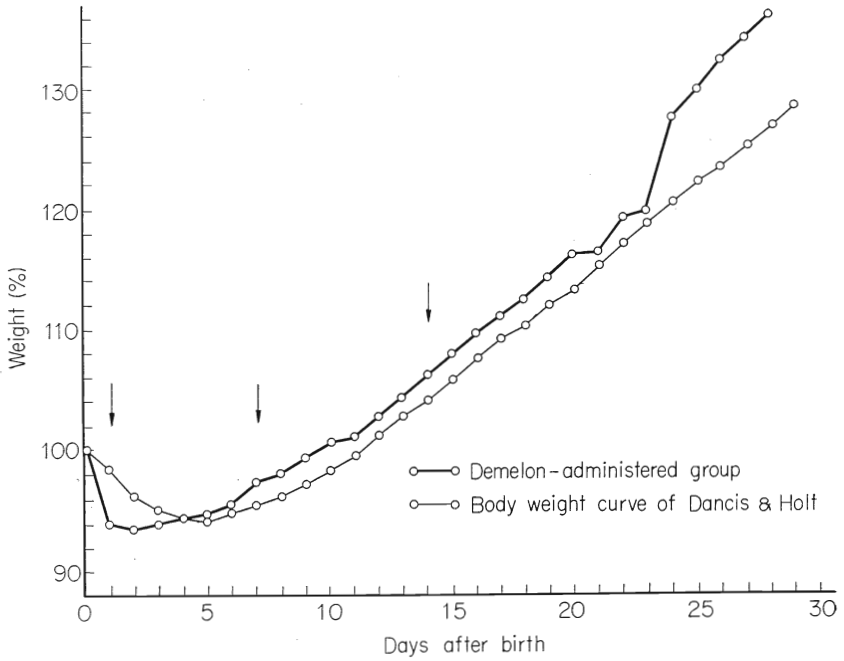

Fig. 1a. Variation in Weight of Babies Weighing 1751-2000 g.

adequate, comparison was made only with the weight curve of Dancis, O'Connell and Holt, while the curve of amount of milk was given only for the experimental group.

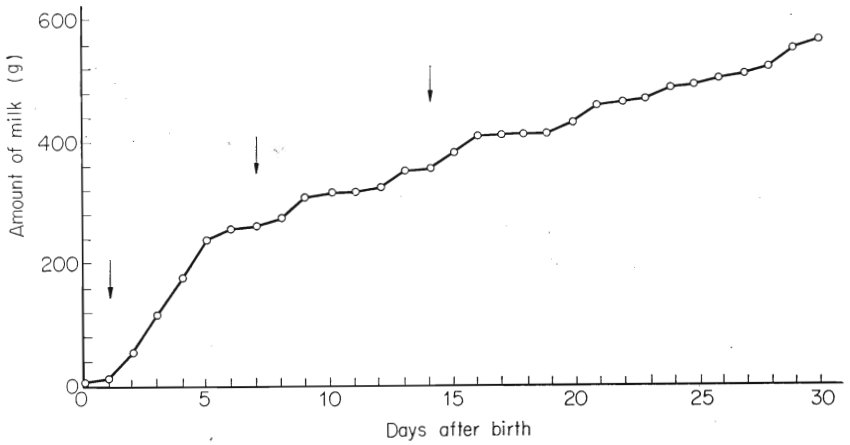

Fig. 1b. Variation in Amount of Milk of Babies Weighing 1751-2000 g.

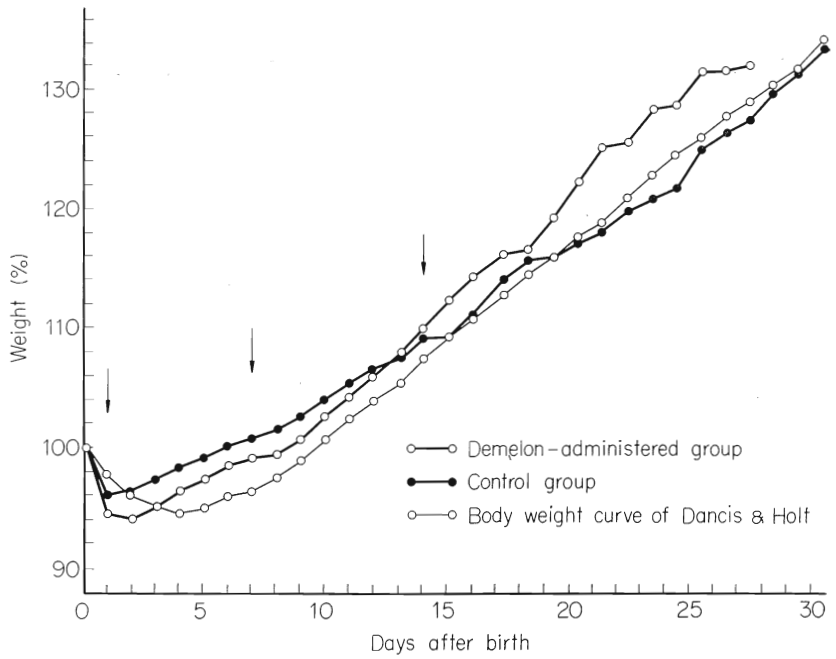

Fig. 2a. Variation in Weight of Babies Weighing 2251-2500 g.

5) Effect of Demelon on the Separation of the Umbilical Cord:

The following table shows a comparison made between the experimental group and the control group in relation to the number of days required for the Separation of the Umbilical Cord.

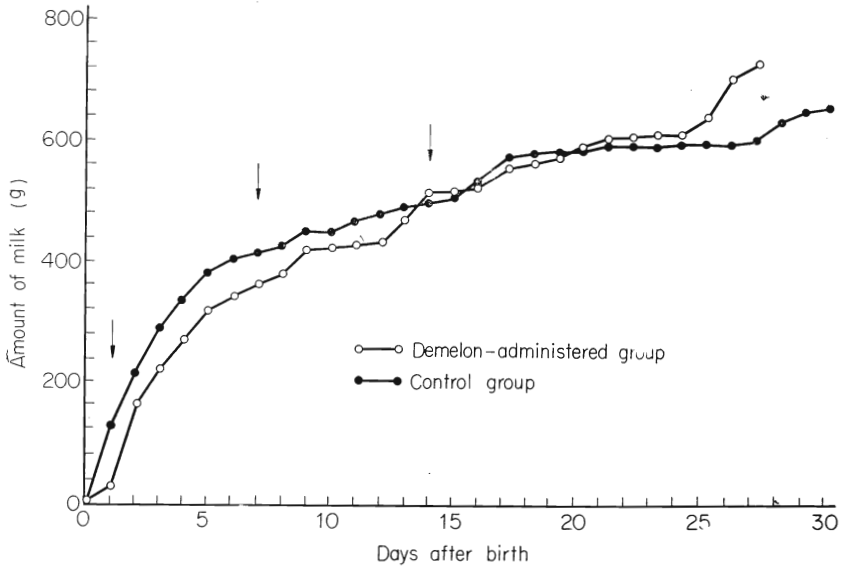

Fig. 2b. Variation in Amount of Milk of Babies Weighing 2251-2500 g.

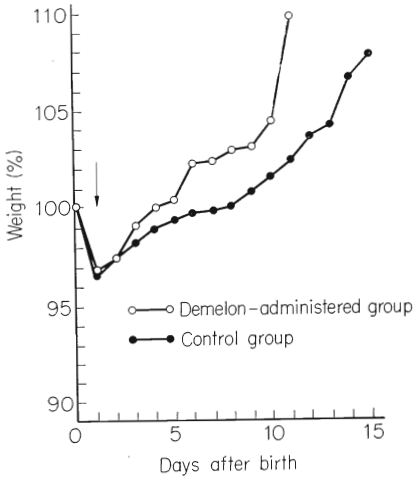

Fig. 3a. Variation in Weight of Babies Weighing 3251-3500 g.

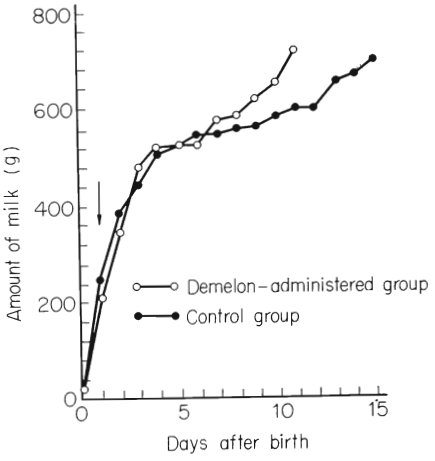

Fig. 3b. Variation in Amount of Milk of Babies Weighing 3251-3500 g.

There is a general trend that in the babies weighing over 2501 g the Demelon group took somewhat more days than the control group for Separation of the Umbilical Cord. For babies weighing less than 2250 g, however, there was a reversed trend for a shorter period. There was not given any convincing cause of this phenomenon.

Table 6. Average Number of Days for Separation of Umbilical Cord

Weight at Birth (g) for Each Subgroup	Demelon Group	Control Group
	Number of Days for Separation of Umbilical Cord	
4001—4250		6.1
3751—4000		5.1
3501—3750	7.0	6.2
3251—3500	6.7	5.7
3001—3250	6.3	6.5
2751—3000	6.4	5.6
2501—2750	5.7	5.8
2251—2500	6.7	6.2
2001—2250	5.6	7.1
1751—2000	8.0	10.5
1501—1750	11.0	

It is to be added that the number of days for the Separation of the Umbilical Cord was expressed by the average number of days in each case.

6) Side Effects:

At least in the range of given dosages of Demelon, there were found no such untoward effects as signs of masculinity, edema, abnormality in the injected region, and the aggravation of jaundice.

V. Conclusion

Since it is difficult to maintain constant condition for the newborn babies subjected to our experiment, and also because of the considerable variation in physiological factors of individual cases, it is extremely hard to give a decisive judgement on the effect of anabolic steroids on newborn babies. However, as far as the above-mentioned method was regarded to be valid, there could be no possible doubt as to the favourable effects of 19-nortestosterone furylpropionate on the increase in body weight, the number of days required for the recovery of weight at birth, the amount of milk, and other factors of newborn babies.

No unanimity has yet been reached in the medical field as to the advisability of the use of anabolic steroids for strengthening the vital force of immature babies and also for promoting their adaptation to the environmental conditions after birth. There are as many objections as approvals in this respect. The essential requirement of immature babies is to have their vitality strengthened, and so it is never sufficient to give them merely an increase in body weight. There are many problems left unsolved with

regard to the use of anabolic steroids for immature babies, such as whether the growth of their body runs parallel with the increase in body weight, whether premature closing of epiphysis should not occur, whether the increase in body weight should not be caused merely by the accumulation of water, whether hepatic trouble should not be feared, and how much would be the appropriate dosage if anabolic steroids are recommendable. It is expected, however, that these problems will be clarified one after another with the advance of clinical investigations.

References

Dancis, O'Connell & Holt: J. Pediat., **33**, 570 (1948).
Eisenberg, E. & Gordan, G.: J. Clin. Endocrinol., **11**, 209 (1951).
Junkmann, K. & Suchowsky, G.: Acta Endocrinol., **36**, 68 (1962).
Schwarting, G. & Neth, R.: Schweiz. Med. Wschr., **90**, 1092 (1960).
Schedl, H. P., Delea, C. & Bartter, F. C.: J. Clin. Endocrinol., **19**, 921 (1959).