decapitation. NA was measured by a fluorimetric method[10] in eluates obtained from alumina columns. An open-field test was used to evaluate the running activity of rats. The apparatus briefly consisted of a black square, 1 m in diameter divided into 16 compartments. The activity was represented by the total number of squares (25 cm² each) traversed during periods of 3 min. Prenylamine-treated and control animals were tested before and at different times after injection of the drug or the vehicle. Differences between groups were considered significant when $P < 0.05$ employing the Student's t-test.

Results. Locomotor activity. It is obvious from Table 1 that the motor activity scores of controls displayed a wide variation from 1 experiment to another. This fluctuation may be attributed to the influence of ambient conditions and spontaneous fluctuations as was previously observed by other authors[8]. In consequence, to examine the effects of prenylamine, controls and drug-treated rats were simultaneously tested in each experiment.

Prenylamine gluconate injected s.c. at doses of 25 and 50 mg/kg produced signs of sedation and a significant decrease of scores (about a 200% decrease) in the open-field test. Sedation began within 1 h and remained during the 6 h of observation. Prenylamine injected at doses of 10 mg/kg caused a 50% decrease of locomotor activity 4 h after injection as shown in Table I but no obvious changes were observed within 1 h.

Noradrenaline content. Concentration of noradrenaline in hypothalamus was reduced at 1,4 and 6 h after injection of 25 and 50 mg/kg of prenylamine (Table II). No differences in hypothalamic noradrenaline between controls and treated rats with 10 mg/kg were detected at 1 h period. In the following hours, a slight decrease took place. NA levels in the cerebral cortex were reduced with the highest doses. Instead, in animals treated with 10 mg/kg NA concentration was normal 1 h before sacrifice; longer intervals (6 h) were required to show a decrease. Thalamic NA fell with doses of 25 and 50 mg/kg. No changes in NA of mesencephalic tegmentum were observed with the 3 different doses of prenylamine employed.

Comments. Our results give further information on relationships between brain NA levels and locomotor activity. The role of DA remains to be evaluated Prenylamine, a drug which depletes brain NA causes, at the same time a marked decrease of motility as shown by the open-field test. According to these data such correlation is more close when hypothalamic NA concentration is related to locomotor activity scores. Fall of hypothalamic NA after prenylamine administration has been previously reported[7]. In the other cerebral regions studied, a reduction in NA levels did not correspond to changes in motor activity. It is probable that modifications of hypothalamic NA have functional significance in the control of sponta neous activity. In this connection, it was recently reported that localization of minute amounts of NA into the hypothalamus induces hyperactivity in rats[11,12].

Resumen. Ratas inyectadas con diferentes dosis de prenylamina (gluconato) presentaron una marcada disminución de la actividad motora espontánea y de los niveles de noradrenalina en el hipotálamo, tálamo y corteza cerebral, pero no en el tegmento del mesencéfalo. Se detectó una estrecha relación entre la caída de la concentración de NA hipotalámica y la disminución de la actividad espontanea con las diferentes dosis de prenylamina empleadas.

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The Effect of Oxymetholone on Tissue Replacement in the Rabbit's Ear

Male sex hormones affect protein metabolism and promote the growth of muscle and bone. They can also stimulate the production of new tissue at sites of injury[1]. The risk of virilization limits the use of such substances and new anabolic drugs have been synthesized in an attempt to reduce androgenic effects while retaining anabolic properties. The clinical efficacy of these compounds as anabolic agents has been reviewed by MOLDAWER[2]. One such drug is oxymetholone (2-hydroxymethylene-17α-methyl-17β-hydroxy-5α-androstan-3-one). It has an advantage in that it can be administered orally. It is structurally related to testosterone but has a higher anabolic effect and an androgenicity of only 1/7th that of testosterone[3].

Material and methods. The effect of oxymetholone on tissue replacement has been tested using the rabbit's ear as the replacement site. If a hole, 1 cm square, is made through the full thickness of the external ear and the tissue completely removed, the tissue removed is replaced by skin and elastic cartilage. The growth of the new tissue can be measured throughout the replacement period without causing further trauma. The technique used involves the calculation of the surface area of the new tissue and has been described elsewhere[4]. All areas are recorded as percentages of the initial lesion to aid comparison.

Tissue was removed from the ears of adult rabbits under pentobarbitone anaesthesia. 3 groups of rabbits were given oxymetholone in distilled water (5 mg/ml) 5 times each week. The dose was 5 mg/3 kg initial body weight. In the first group (4 females) the steroid was administered by stomach tube. This procedure was very stressful and the other groups, 1 of 6 males and 1 of 6 females, were given the steroid into the buccopharynx. A group of control females was given 1 ml/3 kg body weight of the carrier by the same route. There were 2 untreated control groups, 1

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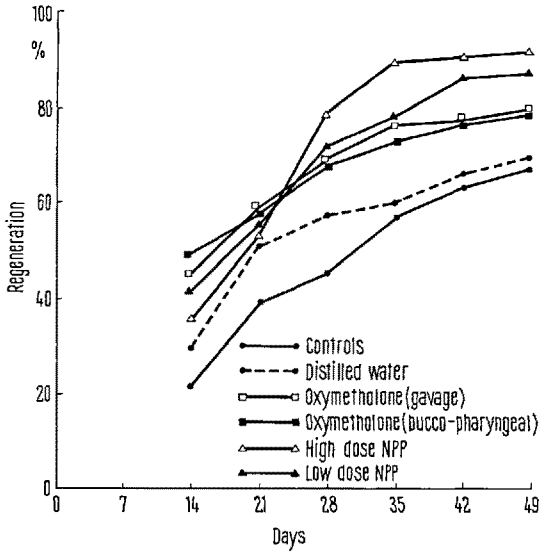

Fig. 1. The effect of oxymetholone and nandrolone phenyl propionate on regenerative growth in females.

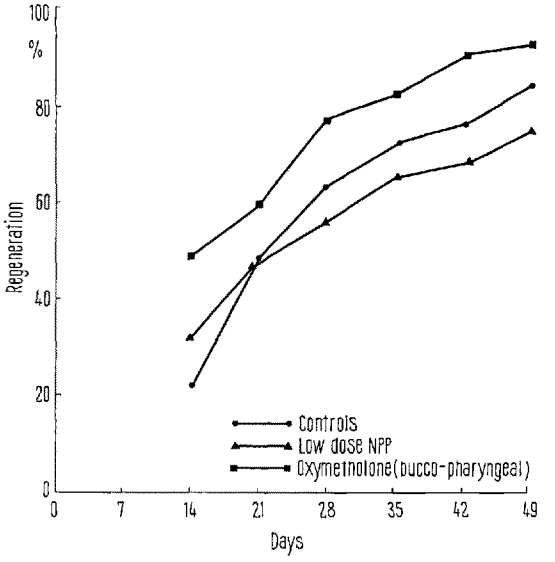

Fig. 2. The effect of oxymetholone and nandrolone phenyl propionate on regenerative growth in males.

of 12 females and 1 of 18 males. The surface area of the new tissue was measured at 7 day intervals from 14 to 49 days. The body weight changes were recorded during the experiment. At 49 days the new ear tissue, liver, kidney, spleen adrenal and either the testis or the ovary and uterus, were examined by light microscopy.

Results. The effects of oxymetholone on regenerative growth are shown in Figures 1 and 2. For comparison the effects of treatment with another anabolic steroid, nandrolone phenyl propionate (NPP) are also shown[1].

The effects of the 2 compounds, NPP and oxymetholone, differed considerably in males and females, as the graphs indicate. The two methods of administration of oxymetholone did not affect the regenerative rate differently in female rabbits. The stomach tube method was therefore abandoned. Administration of the oxymetholone carrier (distilled water) by the buccopharyngeal method did not affect the rate of regeneration significantly, though it did raise it slightly (Figure 1).

In females, both oxymetholone and NPP significantly enhanced the regenerative process. Although at 14 days the effect produced by oxymetholone was slightly in excess of that produced by NPP (at both dose levels), this difference was not significant. By 49 days the situation was reversed but again the difference was not significant ($0.2 > P > 0.1$) because of the wide variation within the 2 groups and the considerable overlap between them.

Oxymetholone stimulated growth significantly in the early stages of regeneration. At 14 days the mean area of the regenerates of rabbits treated with oxymetholone was significantly greater than that of the untreated group ($0.01 > P > 0.001$). The effect was, however, unlike that of NPP in that the initially elevated growth rate was not maintained. By 49 days the difference between the mean growth rate in the untreated controls and that in the rabbits treated with oxymetholone was not significant ($0.3 > P > 0.2$ for both routes of administration).

The effect of oxymetholone on regeneration rate in males is shown in Figure 2. There was a significant increase in regeneration rate at 14 days ($P < 0.001$) but by 49 days the difference between the two groups was no longer significant. However, this latter result is somewhat misleading, for the experimental group completed regeneration earlier than the controls (by 42 days) and in the remainder of the experimental period the control group of untreated males caught up with them. Oxymetholone had a significantly greater effect on regenerative growth than NPP throughout the process. At 14 days, the mean increase in growth was 16.7% higher in the oxymetholone series as compared with the NPP group, and at 49 days the difference was 17.2%. In the experiment in which the males were given low dose NPP there was no significant effect on the rate of regenerative growth[1]. Histological examination of the organs showed no abnormalities.

Discussion. It appears from these results that tissue regeneration takes place more quickly with the administration of oxymetholone. Although this type of regeneration is not strictly comparable with the healing of incised surgical wounds, in which there is little tissue replacement, many wounds have tissue loss which is comparable with the defect in the rabbit's ear in these experiments. There is evidence that oxymetholone, particularly in the early stages in males, is more effective than nandrolone in the replacement of tissue. This may be due to the NPP depressing the production of gonadotrophins and thus effectively lowering the level of endogenous androgen. Animal (rat) studies on oxymetholone have shown that it lacks gonadotrophin inhibitory activity except at very high dosage.

Résumé. L'oxymétholone est un androgène synthétique qui stimule la régénération des tissus. Son action est plus efficace que celle du phényl-propionate-nandrolone, car elle produit le replacement des tissus dès les premiers stades de la régénération chez les mâles. De plus, elle a l'avantage de pouvoir être administrée oralement.

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