

Effects of Adrenalectomy, Thyroidectomy, Thyro-adrenalectomy and Cortisone on Eruption Rate of Incisors in Adult Female Rats.* (26598)

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It has been known that the rate of eruption of the continuously erupting incisor in rats is severely retarded following hypophysectomy(1,2). Growth hormone(1,3) was observed to be ineffective, whereas thyroxine(3) and cortisone(4) were effective in restoring the rate in hypophysectomized rats and in accelerating it in normal rats(4,6,7). Thyroidectomy(8), propylthiouracil treatment(5), and adrenalectomy(4,7) were found to result in a decrease in eruption rate although not so severe as that observed following hypophysectomy. The severity of retardation in eruption rate noted in thyroidectomized rats was observed to be accentuated by a lack of salt in the diet(9). Parathyroidectomy and administration of parathyroid extract had no effect on eruption rate of incisors cut out of occlusal contact(10). The parathyroids are believed to have no effect on incisor eruption rate(11).

There is considerable evidence to indicate that the adrenals and the thyroids play an important role in the process of eruption of the incisors but there is little information to suggest the nature of this role. The present experiments were designed to determine and compare the effects of adrenalectomy, thyroidectomy, and thyro-adrenalectomy, with or without cortisone‡ treatment, on rate of eruption of incisors in young adult rats.

Procedures. Weekly observations were made on eruption rates of maxillary incisors in 28 thyro-parathyroidectomized and 21 intact, female, Sprague-Dawley, albino rats, beginning age 90 days. After 8 weeks, 16 of the thyroidectomized and 11 of the normals were adrenalectomized and maintained on 1% NaCl in the drinking water and observa-

tions continued for a second 8 week period. At the end of the second period, each of the 4 groups was subdivided into a treated and a control group and the experiment continued for a third period of 6 weeks. Treated rats received daily injections of 1.5 mg cortisone and were maintained on tap water while controls were continued without change. The experiment was terminated at the end of the sixth week of period III.

All animals were maintained on a diet of Purina Dog Chow pellets and tap water or tap water with NaCl *ad libitum*. Weekly eruption rates of upper incisors were determined by a method previously described (8, 11). Weekly averages for the first 16 weeks were analyzed by means of the t-test. The F-test was utilized in analyzing averages for each of the 3 periods and to make inter-group comparisons. Source of error used in the F-test was the "within group Mean Square."

Three of the 11 adrenalectomized and 5 of the 15 thyro-adrenalectomized rats were found to have adrenal rests following histological examination of suspicious tissue found on post-mortem. Comparison of eruption rates in adrenalectomized rats possessing adrenal rests, with those of completely adrenalectomized rats, revealed a significant difference but there was no significant difference in response of eruption rates to cortisone treatment. Consequently, weekly eruption rates of adrenalectomized rats possessing adrenal rests on post-mortem were not included in the calculation of averages, excepting those of the 2 cortisone-treated groups.

Serial sections of the thyroid region of tracheas of thyroidectomized rats were examined, and of 20 such examinations considered as adequate, 9 were found to have microscopic rests of thyroid tissue. Evaluation of individual incisor growth rates

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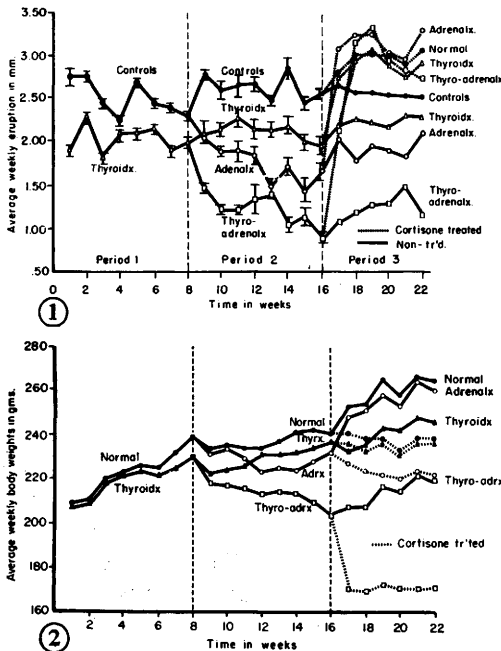


FIG. 1. Avg weekly eruption rates of maxillary incisors in thyroidectomized, adrenalectomized and thyro-adrenalectomized rats with and without cortisone administration. Vertical lines represent the stand. error of the mean.

FIG. 2. Effects of thyroidectomy, adrenalectomy, thyro-adrenalectomy and cortisone administration on body wt.

showed no consistent correlation between the presence or absence of thyroid rests and the eruption rates in many of the animals. Due to the difficulty of assessing the functional capacity of this tissue, it was decided not to exclude any of the thyroidectomized rats from the data, but to report averages for the total group and for the group determined complete by post-mortem histological examination.

Results. The data are summarized in Fig. 1. Thyroidectomy resulted in a highly significant ($P = .001$) reduction of 30% in eruption rates by the end of the first week. Rates showed considerable fluctuation during the first 4 weeks but thereafter tended to remain fairly constant at approximately 20% below normal. Differences between groups proved to be highly significant for each week except the fourth, when eruption rates of normal controls decreased temporarily. The difference observed at this time was not significant

($P = > .05$). The average eruption rate for the first 8 weeks was $2.03 \pm .37$ mm[§] (224 observations, $P = .001$), 19% below that of normal controls whose average was $2.51 \pm .32$ mm (168 observations). The average eruption rate during this period for 9 thyroidectomized rats possessing thyroid rests was $2.12 \pm .38$ mm and for 11 believed to be complete $1.91 \pm .37$ mm (24% reduction). The differences between means of these 2 groups, although small, was found to be highly significant, as were differences between the averages of each of the groups and the normal controls.

During the second 8-week period eruption rates of thyroidectomized rats continued to maintain a fairly constant level at approximately 18% below normal. The average for the second period was $2.15 \pm .36$ mm (96 observations, $P = .001$) as compared with $2.63 \pm .30$ mm (80 observations) for controls. Weekly averages of 7 thyroidectomized rats, verified as complete, showed essentially the same pattern. The average of this group for the second period was 2.02 mm (23% reduction). Adrenalectomy alone at this time, resulted in a highly significant decrease in rate (25%) by the end of the first week. The decrease became progressively more pronounced during the following 7 weeks but thereafter was less pronounced. Average rate for the second period was $1.75 \pm .33$ mm (64 observations, $P = .001$), 33% below that of normal controls. When adrenalectomy was superimposed on thyroidectomy, eruption rates became progressively more depressed, to 65% below normal by the eighth week post-operatively. The average 8-week eruption rate was $1.23 \pm .30$ mm (64 observations, $P = .001$), 53% below normal. All weekly comparisons between normal controls and each of the operated groups were significant ($P =$ or $< .05$). The presence or absence of thyroid rests apparently had little effect on degree of reduction following the second operation (adrenalectomy) since rats possessing thyroid rests showed the same, or a more severe, reduction than those verified as complete.

§ Standard deviation

TABLE I. Summary of Effects on Eruption Rates during Period III of Experiment.

Groups	Mean	S.D.*	% of normal	No. of observations
Normal	2.57	.21	100	30
" + cortisone	2.97	.23	116	30
Adrenalectomy	1.95	.19	76	26
" + cortisone	3.16	.36	123	24
Thyroidectomy	2.25	.20	88	36
" + cortisone	2.89	.24	113	36
Thyro-adrenalectomy	1.26	.27	49	24
" + cortisone	2.86	.41	111	30

* Stand. dev.

In comparing the 8-week averages for period II, the sum of the reductions noted, in thyroidectomized and adrenalectomized groups, was 51% which closely approximated the actual reduction (53%) observed in the thyro-adrenalectomized group. The pooled variation of the thyro-adrenalectomized and normal groups was compared with the pooled variation of the adrenalectomized and thyroidectomized groups utilizing the F-test. The difference was not significant ($F = < 1$), which was interpreted to indicate that there had been no interaction and that the effects of the combined operations equaled the sum of the effects of each operation. Additional comparisons showed a highly significant ($P = .001$) difference between each of the operated groups.

The results for period III are summarized in Table I. During period III eruption rates of the 3 non-treated surgical groups showed a slight increase over previous rates for period II, while rates of the normal controls remained about the same. Administration of cortisone resulted in highly significant increases in eruption rates of all 4 groups to levels above that of non-treated intact rats. The cortisone-treated, adrenalectomized, group showed significantly greater increases than any of the other cortisone-treated groups. There were no significant differences between the responses of the other 3 groups during this period.

Weekly body weights of thyroidectomized and adrenalectomized rats (Fig. 2) fluctuated within a narrow range, somewhat below that of normals. Average weights of thyroidectomized and adrenalectomized rats were

respectively 1% and 3% below those of normal controls by the end of period II and 7% and 1% at the end of period III. Removal of both glands resulted in a progressive decrease in body weight so that averages were 15% and 16% below those of controls by the end of periods II and III respectively. Cortisone administration resulted in weight losses in all 4 groups which averaged 10% in thyroidectomized and intact rats, 16% in adrenalectomized and 35% in thyro-adrenalectomized by the end of period III.

Adrenal weights of cortisone-treated, intact rats (Avg. 43.8 ± 4.4 mg) were reduced to approximately the same degree as those of thyroidectomized rats (Av. 44.3 ± 4.6 mg). Cortisone treatment in thyroidectomized rats brought about further reductions in adrenal weights (Av. 33.5 ± 6.5 mg). The average weight of adrenals in normal controls was 65.3 ± 8.2 mg.

The small number of rats used in each group of period III did not permit adequate evaluation of the effects of thyroid rests; however, they appeared to have little effect on eruption rates. Adrenals tended to be slightly heavier in non-treated, thyroidectomized rats possessing thyroid rests.

Discussion. Close agreement was observed between average eruption rate of normals in each of the 3 periods and normal averages previously reported(2,7). The 33% reduction in eruption rate observed following adrenalectomy closely approximates the 31% reduction reported by us for young rats (7) and the 31% reported by others(4). However, the reduction in rate following thyroidectomy, either during the early

post-operative period or throughout the experiment, or in rats with no discernible thyroid tissue, was not so severe as the reduction previously reported by others following thyroidectomy at birth (45%)(8), or following administration of a "thyroid-blocking" agent (48%)(5). While age could account for the difference in rate in the first instance it does not apply in the second. Whether different strains have different rates has not been determined.

In the present experiments, evaluation of the thyroid status of the animals was difficult. We were unable to find any substantial effect, due to presence or absence of thyroid rests, on incisor eruption rate or body weight. Differences were usually small and inconsistent. Observations have been reported(12) to indicate that there is a decrease in the thyroxin requirements of older animals. Preliminary observations on immature, thyroidectomized rats have shown a more severe reduction in incisor eruption rate than that observed in the present older series which would seem to provide support for the above observation.

We may tentatively conclude that where adrenalectomy is superimposed on thyroidectomy, in young adults, the effects are additive. The resulting cumulative depression in eruption rates closely approximated that previously reported(2) a few weeks after hypophysectomy. However, our thyro-adrenalectomized rats did not show the progressive depression in eruption rate following the eighth week that has been reported by others following hypophysectomy(1,2). Whether the presence of hidden thyroid remnants, age of the animals, or other factors are responsible for this difference in response remains to be determined. The results suggest that the severe depression in incisor eruption rate reported following hypophysectomy(1,2) may be the result of a reduction in available thyroid and adrenal hormones.

In earlier experiments(7) adrenalectomy in young rats brought about little change in body weight during the first few weeks following operation, a period during which eruption rates were severely depressed. The present observations following endocrine removal

might be interpreted as indicating a correlation between weight loss and reduction in eruption rate. However, cortisone administration in these animals resulted in weight losses in all groups, yet despite this loss significant increases in eruption rates were observed. Thyroxin(3) and desiccated thyroid (5) administration also stimulate incisor eruption rates yet desiccated thyroid and cortisone have been reported(13) to be "antagonistic" in their effects on food consumption and body weight in intact rats.

That body weight cannot be considered as a significant factor in regulation of the incisor eruption rate seems indicated from the above results as well as from earlier work(14) where cortisone administration brought about precocious eruption of incisors in new born rats despite severe weight loss. Preliminary observations on dietary restriction, in which severe weight loss was observed, have shown no decrease in eruption rate, verifying the observations of others(10).

The manner in which cortisone acts on eruption rate remains to be determined. Histological and histochemical studies may clarify some of these problems.

Summary. The eruption rate of maxillary incisors was determined in normal, thyroidectomized, adrenalectomized and thyro-adrenalectomized, adult, female rats, with or without daily administration of cortisone. Thyroidectomy resulted in an average reduction in rate of 19% during the first 8 weeks. When adrenalectomy was superimposed on thyroidectomy 8 weeks post-operatively, average rate decreased to 53% below normals, indicating a cumulative effect. Adrenalectomy alone at this time resulted in a 33% average decrease. Administration of cortisone increased the rates in all 4 groups to levels above that of normal controls. The results suggest that the normal rate of eruption of the incisor may be influenced by a synergistic action of the thyroid and adrenal hormones.

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A Neuropharmacological Investigation of the Convulsant Action of 4-Phenyl-4-Formyl-N-Methyl Piperidine (1762 IS)* (26599)

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During an investigation of a series of compounds synthesized for possible strychnine-like activity, one in particular, 4-phenyl-4-formyl-N-methyl-piperidine (1762 IS), was found to possess marked activity as indicated by preliminary screening (1).

In the present work, a more detailed analysis of the action of 1762 IS was made. The usual pharmacological procedures were used as well as more specific technics which included a study of the modifications of the electrical activity at the various levels of the cerebro-spinal axis, the effects of application of the substance to the cerebral and cerebellar cortex on the cortical electrical activity and its action on spinal integratory mechanisms.

Material and methods. Acute toxicity was determined by intraperitoneal and oral administration in mice and intravenously in rabbits. The LD₅₀ was determined in mice using the probit method.

Eleven unanesthetized rabbits paralyzed with 5 mg/kg of gallamine intravenously were used for registration of the cortical and subcortical electrical activity according to a method described previously (2). In all ani-

mals arterial blood pressure was simultaneously recorded. Histological sections were prepared routinely to verify the exact location of the electrodes in the subcortical structures. Experiments in which the compound was applied topically were carried out in 8 rabbits unanesthetized and without neuromuscular paralysis. Disks soaked in various concentrations of the drug were applied on the sensorimotor area of the cortex and on the *lobulus medianus* of the cerebellum. Freshly made water solutions of the hydrochloride salt were used; the dosage is given in weight of the free base.

Experiments on the action of the drug upon the spinal cord were carried out in spinal (Th-10) cats lightly anesthetized with chloralose. After lumbar laminectomy, the appropriate ventral roots were cut and mounted on silver electrodes for recording purposes. The spinal cord was covered with warm paraffin oil. Mono- and polysynaptic reflexes were evoked by stimulation of the popliteal branch of the sciatic nerve. In the experiments dealing with the "primary" inhibition, a maximal monosynaptic reflex was evoked by stimulation of the central stump of the biceps and semi-tendinous nerves (BST). Inhibition of this reflex was obtained by stimulating the group Ia afferent fibers of the quadriceps

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