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The Effects of Various Endocrine Disturbances on the Rate of Eruption and the Histology of the Maxillary Incisor in the Female Albino Rat

Wilbur Arthur Wellband
Loyola University Chicago

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THE EFFECTS OF VARIOUS ENDOCRINE DISTURBANCES ON THE RATE
OF ERUPTION AND THE HISTOLOGY OF THE MAXILLARY
INCISOR IN THE FEMALE ALBINO RAT

by

Wilbur Arthur Wellband

A Thesis Submitted to the Faculty of the Graduate School
of Loyola University in Partial Fulfillment of
the Requirements for the Degree of
Doctor of Philosophy

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LIFE

Wilbur Arthur Wellband was born in Regina, Saskatchewan, Canada, on July 11, 1931.

He was graduated from Central High School, June, 1950. He attended Regina College, the University of Saskatchewan, and George Williams College, Chicago, Illinois, where he received the degrees of Bachelor of Science and Master of Science in December, 1954, and June, 1956, respectively. During his graduate training at George Williams College he was the recipient of the Henry D. Steinhaus Scholarship.

In September, 1956, he began his graduate studies in the Department of Anatomy, Stritch School of Medicine, Loyola University, and was awarded a United States Public Health Service Predoctoral Fellowship during the last two years of his training.

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INTRODUCTION

The term, eruption, denotes several phenomena. Generally, it is regarded as the axial movement of the tooth from its bony crypt, through the gum, into the oral cavity to a definitive position of normal occlusion. However, in the rat the incisors are characterized by continuous growth or eruption which is essentially equal in rate to the process of abrasion or attrition at the tips. The incisor of the rat, therefore, while showing a slow continuous growth throughout life, does not change appreciably in length from week to week.

Continuously erupting or growing incisors are not unique to the rat. This phenomenon is universal in rodents and lagamorphs and isolated examples of it can be found in marsupials (wombat) and primates (aye-aye). Continuously erupting tusks (canines) are found in the elephant, dugong, narwhal, walrus, hippopotamus, swine, and musk deer and continuously erupting cheek teeth (molars) are found in the lagamorphs and in many rodents (Ness, 1956).

The process of eruption and the histology of the rat incisor have been extensively studied under a wide variety of experimental conditions, which may be loosely categorized as dietary, local or mechanical, and hormonal. It is primarily this last category and its influence on the process of eruption in the rat incisor with which we are here concerned.

It has been known that hypophysectomy brings about a severe reduction in the rate of eruption of the rat incisor. Thyroidectomy has also been observed to produce a decrease in rate, although not so severe as that produced by

hypophysectomy. Conversely, the administration of thyroxin has been shown to produce an increase in the rate of eruption in normal, thyroidectomized and hypophysectomized rats while the administration of growth hormone has no effect on this rate, but has been observed to have a stimulatory effect on the tissues of the incisor. Growth hormone when combined with thyroxin is believed to have a synergistic action on the mechanism of eruption.

The relationship between the adrenal cortex and the eruptive process is largely unknown. Since adrenal function was known to be depressed following hypophysectomy we were interested in determining the effects of adrenalectomy and of hormone administration on the tissues of the incisor and on the process of eruption. Furthermore, the interrelationship of the thyroid and adrenal hormones on eruption and on the histology of the incisor has not been investigated.

During the early work on cortisone it was found to have a stimulatory effect on the rate of eruption of the rat incisor while inhibiting the body growth of the animal. The mechanism responsible for this stimulatory effect has not been definitely established. It was believed that a study of the effects of cortisone administration following removal of some of the endocrines would facilitate the solution of this problem. Furthermore, the nature of the eruptive process is not completely understood. Several theories have been advanced to explain this phenomenon, but despite a great deal of investigative work there is no unanimity of opinion with respect to the factors underlying this mechanism. It was hoped that this investigation would provide additional information with respect to the nature of this process.

REVIEW OF LITERATURE

Keith (1911) was the first to propose a causal relationship between the hormones of the pituitary and thyroid glands and the eruptive process. In the rat, the appearance of incisors and molars was reported to be delayed following thyro-parathyroidectomy at birth by Ziskin, Salmon and Applebaum (1940) and Seow and Simpson (1945). The administration of parathyroid extract in newborn thyro-parathyroidectomized rats had no effect on the retarded tooth eruption observed following this operation (Ziskin et al, 1940). Paynter (1954) reported that the administration of 6-n-propyl-2-thiouracil, a thyroid-blocking drug, in newborn rats delayed the eruption of incisors and molars and Hughes (1944) stated that the administration of thiouracil had no effect on the parathyroid function.

Hoskins (1927) produced precocious eruption of incisors in newborn rats by the injection of acetyl thyroxin. Similar observations were made by Karnofsky and Cronbite (1939) following the injection of thyroxin, whereas the injection of an anterior pituitary extract of known thyrotrophic potency had no effect. Palmer, Katonah and Angrist (1951) studied the effects of several adrenal steroids on the eruption of incisors in infant rats. They observed that cortisone, corticosterone and desoxycorticosterone accelerated the appearance of incisors in the oral cavity while adrenocorticotrophic hormone and pregnenolone had no effect. Cortisone administration resulted in a stunting of body growth but it was the most potent stimulator of the incisor eruption

rate of the hormones tested. Corticosterone and desoxycorticosterone had no effect on body growth. Leroy and Domm (1955) reported that cortisone produced precocious eruption of incisors in young rats when administered to pregnant mothers, when administered directly to the fetus in utero, and when administered in newborn shortly after birth. Goldsmith and Ross (1956) studied the histological and histochemical effects of cortisone on the lower incisors of fetal and newborn rats. They observed that the ameloblasts and odontoblasts of the incisors of fetuses and cortisone-treated mothers showed an increase in alkaline phosphatase and ribonucleic acid. Histologically, cortisone administration in neonatal rats produced a marked capillary dilatation, a thickening of the enamel and dentine and precocious eruption.

Mar-Yohana (1957) observed that cortisone administration in prenatal rats in utero, brought about an increase in the size of the incisors, a hyperemia of the pulpal blood vessels, but no change in the size of the incisor socket. When cortisone was administered to neonatal rats there was a decrease in the size of the incisors and the incisor socket. She was unable to detect any histological change in the odontoblasts, dentine, or enamel as a result of treatment.

Of interest in any discussion on precocious eruption of the incisors in the rat is the work of Rowntree and co-workers. Rowntree, Clark and Hanson (1934) observed that the administration of a thymus extract, in rats and their progeny for four successive generations, produced an accruing acceleration in growth and development. Fourth generation offspring of treated parents possessed erupted incisors and open ears at birth whereas the incisors normally

appeared between the eighth and tenth days and the ears opened at two to three days postnatally in controls. These precocious animals appeared to be as far advanced in development at three days of age as normal rats of 16 to 20 days of age. Einhorn and Rowntree (1938) observed similar results following the homologous transplantation of thymus in normal rats and their offspring.

The growth or rate of eruption of the mature, continuously growing rat incisor has also been studied following endocrine extirpation and replacement therapy. Schour and Van Dyke (1932a, 1932B) were the first to experimentally investigate the influence of the pituitary on the incisors. They observed that the eruption rate became progressively more retarded and finally ceased in hypophysectomized rats. Histological examination revealed atrophy of the enamel epithelium, enamel hypoplasia, replacement of the pulp by dentine, multiple foldings of the dentine and a reduction in the blood supply of the pulp. The pulpal obliteration and multiple foldings were considered pathognomonic. The administration of growth hormone (1932b) produced only a slight increase in the rate of eruption of hypophysectomized rats and had no effect in intact rats. Becks, Collins, Simpson and Evans (1946), utilizing a larger number of animals, studied the histological effects of hypophysectomy in the rat incisor over a longer period. They observed that the frequency of dentinal folding increased with longer post-operative intervals, and that it was not present in all of their operated rats. Incisors with non-folded dentine, 617 days post-operatively, differed only slightly from those of normal controls. These changes were restricted to partial obliteration of the pulp canal, the result of a thickening of the labial and lingual dentine, atrophy of the enamel epi-

thelium, and a decrease in pulpal vascularity. They maintained that the thickening of the labial and lingual dentine, at the expense of the pulp chamber, was the only consistent result observed. Becks, Ray and Evans (1954b) extended the previous study of Becks et al (1946) by studies on incisor eruption rates in hypophysectomized rats following progressively longer intervals and by measurements of x-ray photographs taken at the termination of the experiment. Their observations essentially verified previous observations by others. They also observed that the incisors of hypophysectomized rats ceased to increase in size and that complete cessation of eruption appeared to be related to a conspicuous apical folding of the incisor.

Baume, Becks and Evans (1954a) also reported observations on rat incisors following thyroidectomy at birth, with or without subsequent replacement treatment. In these experiments thyroidectomy was observed to bring about a reduction in eruption rate, although not so severe as that observed following hypophysectomy. Marked reduction in pulpal vascularity, hypercalcification of the dentine and an inhibition in histodifferentiation of incisor tissues were noted. The administration of growth hormone produced a slight increase in eruption rate, in tooth dimensions and an increase in the vascular and cellular connective tissue elements of the pulp. Thyroxin administration brought about a greater acceleration in eruption rate as well as increase in incisor dimensions. It also produced a histologically discernable proliferation and histodifferentiation of the epithelial tissues and an increase in vascularization of the pulp. The simultaneous administration of both hormones resulted in an increase in eruption rate to the same degree as did thyroxin alone and brought

about a histological restoration of the dental tissues. That the thyroid influences eruption of the incisors in the rat has been further substantiated by Garren and Greep (1955) who observed that the feeding of desiccated thyroid produced an acceleration in eruption rate while propylthiouracil brought about a decrease in this rate. Their x-ray studies revealed an increase in dentine per unit area of incisor and a decrease in the dimensions of the pulp chamber as a consequence of propylthiouracil feeding.

In a third series of experiments Baume, Becks and Evans (1954c) studied the effects of thyroxin and growth hormone on eruption rate, histology and radiographic dimensions of incisors in hypophysectomized rats. The administration of growth hormone resulted in a radiographic increase in incisor dimensions but did not accelerate the eruption rate while stimulation of the fibroblasts, without stimulation of amelogenesis, was observed histologically. Thyroxin administration also increased tooth dimensions radiographically, accelerated the eruption rate and brought about hyperplasia of the enamel epithelium. The administration of both hormones restored the various tissue components and accelerated the rate of eruption of the incisors. The authors concluded as a result of their observations that the eruptive process is controlled by the synergistic action of both hormones.

The parathyroids appear to have no influence either on the time of eruption of the incisors in newborn or on the rate of eruption in sexually mature rats. Bryer (1957) reported that neither parathyroidectomy nor the excessive administration of parathyroid extract had any effect on the unimpeded eruption rate of lower incisors cut out of occlusal contact. Schour and Massler (1949),

in reviewing various dietary and endocrine influences on the rat incisor, concluded that the parathyroids were concerned with calcification and the thyroid with growth and eruption.

The relationship of the adrenals to the eruptive process has not been so thoroughly investigated. Schour and Rogoff (1936) studied the histology of the incisors in adrenalectomized rats. They observed a severe disturbance in dentine calcification characterized by the presence of hematoxylin-staining globules in the predentine. These were similar to those observed in the predentine of incisors in rats given parathyroid extract. Due to the short survival period no significant modification in the rate of eruption could be determined. Frey, Genitis, Schour and Templeton (1936) observed that a salt-deficient diet had no effect on the rate of eruption of the incisors in intact rats but they found that it produced a further reduction in rate in thyro-parathyroidectomized animals. Domm and Marzano (1954) and Garren (1954) reported that cortisone accelerated the eruption rate of incisors in intact rats. Repeated injections of cortisone (Glickman and Shklar, 1954) were observed to produce disintegration and necrosis of odontoblasts, a reduction in the number of fibroblasts and a pronounced dilatation of the pulpal blood vessels.

The factors responsible for tooth eruption have never been demonstrated to the complete satisfaction of those most interested in the problem. Constant (1900) was one of the first to suggest a relationship between vascularity and eruption. Since then many investigators have observed an increase in the vascularity of dental tissues which could frequently be correlated with precocious eruption in young animals or an increased eruption rate in adults. Massler and

Schour (1941) reviewed the major theories of tooth eruption and their evidence would seem to indicate that the eruptive force of the tooth is not a growth process, but is dependent upon the vascularity of the tissue which surrounds the tooth. This theory was substantiated by Bryer (1957) who studied a variety of dietary and hormonal effects on the eruption rate of rat incisors cut out of occlusal contact. He was able to correlate reduction or increase in vascularity with reduction or acceleration in eruption rate and concluded that the eruptive force is derived from the pressure within the blood vessels entering the fundus of the incisor and the resulting tissue turgor.

The exact relationship between the vascularity of the rat incisor and its growth rate has been difficult to establish experimentally. Taylor and Butcher (1951) and Miller (1957) reported that sympathectomy had no effect on eruption rate in the rat. However, Bryer (1957), studying incisors cut out of occlusal contact, observed a significant increase in rate of eruption following sympathectomy, which lasted approximately two weeks. Bryer also repeated previous experiments, reported by Massler and Schour (1941), in which the lower incisor was cut out of occlusal contact and a portion of the pulp removed. The rate of eruption in such incisors became severely retarded. If, however, the pulp was replaced by gutta-percha, the rate of eruption fluctuated for two weeks and then returned to normal. When he amputated the basal formative end of the incisor and also cut the tooth out of occlusal contact, the distal end continued to erupt and in some cases exfoliated.

The traumatic type of surgery employed in earlier work was criticized by Sturman (1957) on the ground that the normal conditions within the jaw were al-

tered. He hoped to circumvent this problem by the extra-oral injection of vasostimulating drugs into the pulp cavity of the rat incisor. However, he found that the insertion of the needle into the pulpal cavity increased eruption rates to the same degree as the injection of a vasodilator drug while the injection of a vasoconstrictor drug prevented this increase for one week. He concluded that the eruptive force was probably derived from proliferation of the odontogenic epithelium and pulpal cells, a theory previously proposed by Baume et al (1954c).

Since adrenal function is depressed following hypophysectomy and since the rate of eruption of the rat incisor has been shown to be stimulated by adrenal cortical hormones, the importance of determining the effects of adrenalectomy, of the administration of cortical steroids and of salt substitution treatment, on the rate of eruption and on the histology of the incisor seems obvious. Furthermore, the nature of the relationship between the adrenal and the thyroid in the process of eruption is important and requires further clarification.

MATERIALS AND METHODS

Albino rats of the Sprague-Dawley strain were used throughout these experiments.¹ All animals were maintained on a diet of Purina Dog Chow Pellets or Rockland Mouse Diet and tap water ad libitum. In some of the experiments 1% sodium chloride or 0.1% 6-n-propylthiouracil² was added to the tap water. Weekly observations on body weights and daily observations on the health of the animals were recorded. The hormone used throughout the course of the investigation was cortisone (Cortone acetate).³ The dosage (1.5 mg daily) used in many of the experiments was determined from preliminary observations.

The method employed to measure the rate of eruption had been previously used (Schour and Massler, 1949; Baume et al, 1954a; Sturman, 1957), and is illustrated in Figure 1. It consisted in making a small mark with a jeweler's file, under magnification, on the labial surface of the incisor, opposite the gingival crest. The distance from the mark to the tip or occlusal surface of the tooth was measured and recorded. One week later this distance was again measured and a new mark placed on the tooth at the gingival crest. Careful

¹Purchased from the Hormone Assay Laboratories, Incorporated, Chicago, Illinois. These laboratories also carried out all of the necessary surgical procedures.

²Lederle Laboratories, Division American Cyanamid Company, Chicago.

³Generously supplied to Dr. L. V. Domm by Merck, Sharp and Dohme, Division of Merck and Company.

attention was given to the placement of the mark so as to put it as nearly as possible at the same point, with respect to the gingival crest, each week. The distance the first mark had migrated from the new mark at the gingival crest was recorded as the amount the incisor had erupted or grown during the period between each measurement. Average weekly eruption rates were calculated for each of the groups and analyzed statistically for each week and for each experimental period, utilizing the t-test or the Analysis of Variance Test (Batson, 1956). Differences were considered significant at the 5% level of probability.

The completeness of the operation following adrenalectomy was established by a careful examination at autopsy of the adrenal bed and by a histological examination of any suspicious tissues. The completeness of thyroidectomy was determined by examination of serial sections of the thyroid region of the trachea and, in the case of young animals, by the cessation in weekly body weight gains. Complete hypophysectomy was not established by the customary histological procedure but only by observations on cessation of growth, failure to open or delayed opening of the vagina, and atrophy of thyroids, adrenals, and ovaries.

At the termination of most of the experiments the animals were killed with an overdose of Pentothal Sodium,¹ the heads removed, split sagittally, and fixed in neutral, 2% calcium acetate, in 10% formalin. Maxillary incisors were

¹A product of the Abbott Laboratories, North Chicago, Illinois.

later dissected, decalcified for 20 to 36 hours in an ionic bone decalcifier¹ in a solution of 1% formic acid and 0.8% hydrochloric acid. Tissues were then dehydrated, imbedded in paraffin under vacuum, sectioned sagittally, and stained with Harris' alum hematoxylin or Delafield's alum hematoxylin and eosin.

X-rays² were made of the sagittally split skulls utilizing a standardized procedure which consisted in placing the split skull, cut surface down, upon an occlusal dental film with the cone two inches above. The film was then exposed for one-half second at 10 milliamperes and 65 kilovolts. The roentgenograms were examined under a dissecting microscope at 9x magnification and the following measurements (Figure 2) made on maxillary incisors with the aid of a one millimeter micrometer disc:

1. The width of the incisor at the alveolar crest.
2. The thickness of the labial dentine at the alveolar crest.
3. The inside (lingual) diameter of curvature.
4. The distance between the hard palate and the incisor tip.
5. The distance between the basal or fundus end of the incisor and the first molar.
6. The longest distance from the hard palate at an angle of 90° to the inner surface of the incisor.

¹Manufactured by Martin Sweets Company, Louisville, Kentucky.

²Equipment made available through the generosity of the Department of Orthodontia, Loyola University School of Dentistry, Chicago.

All measurements were made without reference to the type of treatment administered.

A total of nine experiments were performed to observe the effects of adrenalectomy, thyro-parathyroidectomy, thiouracil administration, thyro-adrenalectomy, hypophysectomy, and adrenalectomy with thiouracil administration, with and without cortisone treatment. In addition the effects of unilateral adrenalectomy with contralateral adrenal enucleation and dietary restriction were studied. Observations and treatment were usually started on the day following the operation and in experiments in which cortisone was administered, the respective controls received injections of a similar volume of a 0.9% physiological NaCl solution. The experimental procedures will be discussed in detail later in the thesis.

The histological effects of thiouracil treatment, hypophysectomy and cortisone on mitotic activity in the tissues of the incisor were studied on 10 female rats of various ages, utilizing the colchicine technique. The colchicine¹ was administered at a dosage, recommended by Fleischmann (1939), of 1.0 mg per kilogram of body weight. This was found to be sufficient to arrest mitosis at the metaphase stage. The animals were sacrificed 18 hours later at which time the incisors were removed, fixed in neutral formalin and prepared for histological examination.

¹Colchicum autommale, A product of Eli Lilly and Company, Indianapolis, Indiana.

EXPERIMENTAL RESULTS

A. Incisor Eruption Rates and Gross Observations

1. Adrenalectomy and Cortisone in Young Females

Twenty-four female rats, bilaterally adrenalectomized at 39 days of age and 12 unoperated controls of the same age were studied. Twelve operated and six intact rats received daily injections of 1.5 mg of cortisone, six days per week for six weeks. The remaining animals served as operated and intact controls. Adrenalectomized controls were maintained on drinking water containing 1% sodium chloride. At the end of the sixth week all treatment (daily injections and NaCl in the drinking water) was discontinued and observations continued for a second six-week period. Eruption rates of incompletely adrenalectomized rats surviving throughout the six-week period following cessation of maintenance treatment (3 cases) were eliminated from the data and calculations.

The eruption rates (Figure 3) of adrenalectomized saline-maintained rats showed a significant decrease (-26%) by the end of the first week and a maximum decrease (-30%) during the second and (-32%) third weeks, when compared with normal controls. During the fourth to the sixth weeks there was a slight increase, although the rates were still significantly below normal. The average weekly eruption rate for the first six weeks was 1.84 ± 0.34^1 mm (56 observations; $P = .001$), which was 28% below the average of the normal controls,

¹Standard deviation.

2.56 \pm 0.24 mm (36 observations), and highly significant. Following cessation of treatment eruption rates declined to the level (-26%) observed during the first three weeks after the operation. The average survival time following cessation of saline maintenance in adrenalectomized animals was 6.4 \pm 3.2 days, with only one animal surviving the remainder of the second period in apparent good health.

The body weights (Figure 4) of adrenalectomized rats showed weekly increases equal to those of normal controls up to the third week. Thereafter, weekly increases were less pronounced, so that by the end of the sixth week of treatment they were 11% below those of normal controls. Following cessation of treatment this difference increased to 20% as the animals succumbed of adrenal insufficiency.

The administration of 1.5 mg cortisone produced an increase in the rate of eruption (Figure 3) of adrenalectomized rats, which was found to be statistically significant by the second week and thereafter for the remainder of the six-week period. The average rate of eruption for the period of cortisone administration was 3.08 \pm 0.38 mm (60 observations; P = .001) which was 21% greater than that of normal controls and highly significant. The cessation of cortisone administration was followed by a sharp decline in the rate of eruption, so that by the third week of the second period rates were 40% below normal at which time the animals were dying of adrenal insufficiency. The average survival time following cortisone withdrawal was 22.1 \pm 5.3 days, a highly significant difference from the survival time of those maintained on saline. Two animals survived the remainder of the second six-week period.

Cortisone administration produced a severe reduction in body weight (Figure 4) so that by the end of the first six-week period treated adrenalectomized rats were 40% below the average of normal controls. Cessation of treatment did not appreciably affect the body weight, and growth remained severely retarded to the time of death at the end of the third week of the second period.

The administration of cortisone in intact rats produced a slight increase in eruption rate (Figure 3), which proved to be statistically significant only during the second week (-20%). The average rate for the six-week period of treatment was 2.82 ± 0.30 mm (36 observations; $P = < .2$), which was 10% greater than that of normal controls, but not significant. Following cessation of treatment eruption rates declined below those of normal controls and remained below normal for the remainder of the second six-week period. This reduction was statistically significant during the eighth, ninth and twelfth weeks. However, the average rate (2.21 ± 0.32 mm) for the second six-week period did not differ significantly from the average for the controls (2.46 ± 0.27 mm).

Cortisone administration in intact rats resulted in a reduction in body weight of 14% below that of normal controls by the end of six weeks. This loss in weight was quickly regained following cessation of treatment. There was no significant difference at autopsy, six weeks after cessation of treatment, in the weights of the adrenals of treated and control rats.

2. Adrenalectomy, Cortisone, and Saline in Young Males

Twenty-one male rats, adrenalectomized at 39 days of age, and 12 unoperated

controls were divided into the following five groups: 7 adrenalectomized maintained on water, 7 adrenalectomized maintained on 1% NaCl, 7 adrenalectomized receiving cortisone treatment and maintained on water, 6 unoperated normal controls and 6 unoperated receiving cortisone treatment. Cortisone was administered twice daily, six days a week, in a divided dosage of 0.75 mg in the morning and 0.75 mg in the late afternoon. The experiment was terminated at the end of two weeks.

The results of the experiment are summarized in Table I. Adrenalectomy, without salt maintenance, resulted in a highly significant 32% decrease in eruption rate and the death of all seven animals. The average survival time of these rats was 6.6 ± 1.9 days. The addition of 1% sodium chloride to the drinking water did not appreciably influence the effects of adrenalectomy on eruption rate. Eruption rates of saline-maintained rats were significantly depressed to 25% below that of normal controls. The small difference in rates between these two adrenalectomized groups was not significant. Three of the seven saline-maintained operated animals survived the 15 day period of observation. The average survival time of the other four was 7.3 ± 3.8 days, and was not significantly different from that of operated rats maintained on water.

The administration of cortisone resulted in a highly significant increase in eruption rates in both intact and operated rats. In many cases the markings at the distal end of the incisors were lost due to this marked increase in growth and attrition. As a result the rates of these two groups were considered as approximations and no attempt was made to analyze the differences in response.

The effects of the various treatments on daily body weight are summarized in Figure 5. The daily weight increments of saline-maintained adrenalectomized rats closely approximated those of normal controls until the tenth day, post-operatively, when a slight decrease in weight occurred. The average body weight of the three surviving animals was only 7% below that of normal controls at the end of the experiment. Body weights of adrenalectomized rats, maintained on water, showed a severe decrease, starting on the third day and clearly evident by the fifth and sixth days, post-operatively. The administration of cortisone, while accelerating the eruption rates of adrenalectomized rats, brought about a depression in body weights to almost the same degree as that produced by adrenal insufficiency. Treated adrenalectomized rats weighed 33% less than normal controls after 15 days of daily cortisone administration, whereas the body weights of treated intact rats were reduced only 12%.

3. Thyroidectomy, Adrenalectomy, Thyro-adrenalectomy and Cortisone in Young Adult Females

Similar observations were made on 28 thyro-parathyroidectomized and 21 intact female rats. The operations were performed when the animals were 90 days of age. After eight weeks 16 of the thyro-parathyroidectomized and 11 normals were adrenalectomized and maintained on drinking water containing 1% NaCl and observations continued for a second eight-week period. At the end of the second period each of the four groups was subdivided into a treated and a control group and the experiment continued for a third period of six 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 treatment.

Three of the 11 adrenalectomized and five of the 15 thyro-adrenalectomized rats were discovered to have adrenal rests, following a histological examination of questionable tissue found at autopsy. A comparison of the eruption rates in adrenalectomized rats possessing adrenal rests with those in which no adrenal rests were found revealed a significant difference, but no significant difference in the response of eruption rates to cortisone treatment. Consequently, the weekly eruption rates of adrenalectomized rats possessing adrenal rests were not included in the calculation of averages, excepting those of the two cortisone-treated groups.

Serial sections of the thyroid site of tracheae of thyroidectomized rats were examined, and of twenty such examinations considered as adequate, nine were found to have microscopic rests of thyroid tissue. Evaluation of individual incisor growth rates 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 in 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, where possible, averages for the group in which no thyroid was found on post-mortem histological examination.

Thyroidectomy resulted in a highly significant reduction (30%) in eruption rates (Figure 6) by the end of the first week. The weekly rates showed considerable fluctuation during the first four weeks, but thereafter tended to remain fairly constant at approximately 20% below normal. The differences

between the two groups proved to be highly significant for each week except the fourth, when the eruption rates of normal controls decreased temporarily. The difference observed at this time was not significant. The average eruption rate for the first eight weeks was $2.03 \pm .37$ mm (224 observations; $P = .001$) which was 19% below that of normal controls whose average was $2.51 \pm .32$ mm (168 observations). The average eruption rate during this period for nine thyroidectomized rats, possessing thyroid rests, was $2.12 \pm .38$ mm and for eleven, in which no thyroid rests were found, $1.91 \pm .37$ mm (24% reduction). The difference between the means of these two thyroidectomized groups, although small, was found to be highly significant, as were differences between the averages for each of the groups and the normal controls.

During the second eight-week period the 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 the controls. The weekly averages of seven thyroidectomized rats, in which no thyroid was found, showed essentially the same pattern. The average of this group for the second period was 2.02 mm which was 23% below the average of normal controls.

Adrenalectomy alone at this time resulted in a 25% decrease in rate by the end of the first week which was highly significant. This decrease became progressively more pronounced during the following seven weeks, but thereafter was less pronounced. The average rate for the second period was $1.75 \pm .33$ mm (64 observations; $P = .001$) which was 33% below that of normal controls.

When adrenalectomy was superimposed on thyroidectomy, eruption rates be-

came progressively more depressed, so that by the eighth week post-operatively they were 65% below normal (Figure 6, Period II). The average eight-week eruption rate was $1.23 \pm .30$ mm (64 observations; $P = .001$) which was 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 the degree of reduction following the second operation (adrenalectomy), since rats possessing thyroid rests in most cases showed the same or a more severe reduction than those in which no thyroid was found.

In comparing the eight-week averages for Period II, the sum of the reductions, noted in the thyroidectomized and the adrenalectomized groups, was 51% which closely approximated the actual reduction of 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 Analysis of Variance Test. The difference was found not to be 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 both operations. Additional comparisons showed a highly significant difference between each of the operated groups.

The results of the third period are summarized in Table II and Figure 6. During this period the eruption rates of the three non-treated surgical groups showed a slight increase over the rates for the preceding period, while the rates of the normal controls remained about the same. The administration of

cortisone resulted in significant increases in the eruption rates of all four groups to levels above that of normal controls. The greatest increase was observed in the cortisone-treated adrenalectomized group, which was significantly ($P = .05$) greater than the increases observed in any of the other cortisone-treated groups (Figure 6). There were no significant differences between the responses of the other three treated groups during this period but highly significant differences were again found between each of the operated groups.

The body weights of thyroidectomized rats (Figure 7) showed little difference from those of normal controls during Periods I and II and only a slight reduction during Period III. The average body weights of thyroidectomized rats were 4%, 1% and 7% below those of normals at the end of each of the three periods, respectively. There was no apparent correlation between body weight and the presence or absence of thyroid tissue. Adrenalectomized rats showed a 3% reduction in body weight by the end of Period II and essentially the same weight as controls at the end of Period III. Thyro-adrenalectomy resulted in a slow progressive loss in weight, so that the averages were 15% and 16% below those of controls by the end of each of the last two periods, respectively. Cortisone administration brought about losses in body weight in all four groups, resulting in a 10% reduction in thyroidectomized and intact rats, a 16% reduction in adrenalectomized and a 35% reduction in thyro-adrenalectomized rats by the end of Period III.

The adrenal weights of cortisone-treated intact rats (Average, 43.8 ± 4.4 mg) were reduced to approximately the same degree (33%) as those of thyroidectomized rats (Average, 44.3 ± 4.6 mg, 32% reduction). Cortisone adminis-

tration in thyroidectomized rats brought about a further reduction in adrenal weights (Average, 33.5 ± 6.5 mg, 49% reduction). The average weight of the adrenals in normal controls was 65.3 ± 8.2 mg. The adrenals appeared to be slightly heavier in non-treated thyroidectomized rats possessing thyroid rests.

The small number of animals used in each of the groups during Period III did not permit an adequate evaluation of the effect of thyroid rests on eruption rate. The averages of nine thyroidectomized rats, verified as complete at autopsy, are included in Table II for comparison.

4. Hypophysectomy and Cortisone

Twenty-two normal females and 20 females, hypophysectomized at 26 days of age, were employed, observations beginning at four weeks following the operation. After eight weeks each group was subdivided into a treated and a control group and observations continued for a second period of seven weeks. Treated rats received 1.5 mg of cortisone daily.

The data are summarized in Figures 8 and 9. Four weeks following the operation the eruption rates of hypophysectomized rats (Figure 8) were 68% below those of normal controls. During the following weeks the rates showed a further, gradual reduction averaging 69% and 72% respectively below normal by the twelfth and nineteenth weeks post-operatively. The average eruption rate for the first period was $0.84 \pm .26$ mm as compared with $2.50 \pm .29$ mm for normal controls ($P = .001$). This was associated with a virtual cessation of body growth. The average body weight of these animals was only about one-half (48%) that of normal 12 weeks after the operation.

The daily administration of 1.5 mg cortisone, beginning 12 weeks post-

operatively, dramatically accelerated the eruption rates to within the normal range. Differences between the means of treated hypophysectomized and normal controls were not significant during the tenth, eleventh, twelfth and fourteenth weeks (14, 15, 16 and 18 weeks post-operatively). However, eruption rates were significantly different during the other three weeks as was the average for the seven-week period. The average rate for the seven weeks of treatment was $2.20 \pm .42$ mm which was 13% below that of normal controls, whose average rate was $2.52 \pm .30$ mm ($P = .001$) and almost three times the rate of non-treated hypophysectomized rats ($0.76 \pm .18$ mm).

The body weights of treated hypophysectomized rats showed a severe reduction, the first indications of which became evident as early as the end of the first week of treatment. (Figure 9), This reduction became more severe with continued treatment and resulted in the loss of 50% of the rats by the seventh week. At this time the average body weight was less than one-third that of normal controls and approximately two-thirds that of operated controls, yet despite this loss in weight eruption rates were accelerated to more than twice that of non-treated operated rats.

Cortisone administration in intact rats produced a significant increase in eruption rate (Figure 8), which was quite evident after one week of injections and which remained significantly accelerated ($P =$ or $< .05$) during the entire period of treatment. Body weights were reduced to an average of 13% below that of normal controls by the end of the seventh week.

At autopsy hypophysectomized rats, which were moribund as a consequence of treatment, revealed large pulmonary abscesses, a finding previously observed

by Selye (1951) and Domm and Leroy (1951) following excessive dosages or prolonged cortisone administration in intact animals. In several cases the abscesses were so extensive that the lung tissue failed to float but sank in the fixative. This condition was rarely observed in any of the other animals.

Adrenal weights showed a significant reduction as a consequence of cortisone administration, averaging 43.1 ± 6.6 mg as compared with 61.4 ± 10.6 mg for the controls. This reduction was not so severe as that observed following hypophysectomy. The average adrenal weight of eight hypophysectomized rats was 11.5 ± 1.62 mg, and 8.6 ± 1.4 mg for three cortisone-treated hypophysectomized rats.

5. Hypophysectomy and Cortisone (Reduced Dosage)

Ten normal unoperated, nine hypophysectomized, ten cortisone-treated unoperated, and twelve cortisone-treated hypophysectomized female rats were used in this experiment. The hypophysectomies were performed at 40 days of age. Treated rats received 0.5 mg of cortisone daily for six weeks, when the dosage was reduced to 0.25 mg and injections continued for another six-week period. Injections and measurements were begun on the day following surgery. Eruption rates of the mandibular incisors were also measured for the first twelve weeks.

Because the mortality rate of treated hypophysectomized rats became so severe they were sacrificed at the end of the tenth week. The normal intact controls and the cortisone-treated intact rats were continued on the same regime for an additional two weeks. At this time the normal control group was subdivided into a treated and a control group, treated rats receiving 1.0 mg

of cortisone daily for six weeks. The previously treated intact group was similarly subdivided into two groups. One continued to receive 0.25 mg cortisone while the other group received the higher dose of 1.0 mg. This last six-week period was designed to determine if changes in sensitivity to cortisone had occurred as a result of the twelve weeks of prior treatment.

The administration of 0.5 mg cortisone in hypophysectomized rats, starting on the day following the operation, maintained incisor eruption rates (Figure 10) within the normal range. This was evidenced statistically (Analysis of Variance Test) by the absence of a statistical significance in differences between the averages of normal controls and those of treated hypophysectomized rats, for each except the fourth week ($P = .001$) of the first period. However, rates were consistently slightly below the normal average (7%) and the difference between averages for the first six weeks proved to be highly significant ($P = .001$). The average rate during this period was $2.42 \pm .30$ mm for treated hypophysectomized animals and $2.62 \pm .24$ mm for intact controls.

The reduction in daily dosage from 0.5 mg to 0.25 mg at the end of the sixth week was accompanied by a corresponding reduction in the accelerated rate of eruption and the average ($1.96 \pm .27$) for Period II was 22% below that of normal controls ($2.53 \pm .22$, Figure 10).

Body weights of treated hypophysectomized rats (Figure 11) again revealed the adverse effects of cortisone, averaging 65% below normals and 32% below hypophysectomized controls by the end of the sixth week of treatment. The reduction in daily dosage to 0.25 mg did not appreciably influence this effect; body weights remained depressed during the four weeks of the second period.

The mortality rate appeared similarly unaffected with 50% (6 of 12 rats) of the animals dying by the end of the eighth week of treatment, compared with a 50% mortality by the end of the seventh week in the previous experiment. Pulmonary abscesses were again consistently observed at autopsy in treated hypophysectomized but not in intact rats. If this was the primary cause of death, then the reduction in dosage at the end of the sixth week of the experiment may have been too late to have had any beneficial effect.

The eruption rates of non-treated hypophysectomized rats were reduced to about one-half (53%) of those of normal controls by the end of the first week following the operation (Figure 10). Following this there was a more gradual reduction in rate, so that by the end of the tenth week the rates were reduced to 63% below normal. The average rate of hypophysectomized rats for Period I was $1.16 \pm .22$ mm and for Period II, $0.93 \pm .19$ mm.

The administration of 0.5 mg cortisone in intact rats resulted in a slight but consistent 7% increase in rate of eruption (Figure 10) which proved to be statistically significant ($P = .001$) for the six-week period. A reduction in the dosage reduced the difference between rates of treated and normal controls to 3% for the six-week period, which did not prove to be significant.

Body weights of intact rats receiving a daily dose of 0.5 mg were reduced to 7% below normal by the end of the sixth week whereas weights were reduced only 2% after six weeks on a daily dosage of 0.25 mg (Figure 11).

The eruption rates of mandibular incisors in hypophysectomized rats (Figure 12) revealed changes corresponding to those observed for the maxillary incisors. However, the mandibular rates did not show so severe a reduction as

did the rates of the maxillary incisors. Mandibular rates were reduced 33% by the end of the first week and averaged 41% below normal for the first period and 49% for the second period. The average rate was $1.95 \pm .35$ mm for the first period and $1.65 \pm .32$ mm for the second, as compared with $3.32 \pm .31$ mm and $3.27 \pm .41$ mm for the controls. These differences were highly significant ($P = .001$).

The daily administration of 0.5 mg cortisone restored mandibular eruption rates in hypophysectomized rats to levels indistinguishable ($P = > .05$) from those of normals (Figure 12). The average for the first six weeks was $3.38 \pm .49$ mm. A reduction in dosage resulted in a corresponding reduction in rate. The average for the four weeks of the second period was $2.97 \pm .55$ mm which was 9% below that of normals and significant ($P = .05$).

Cortisone administration, at a dosage of 0.5 mg per day, produced a highly significant 8% increase in mandibular eruption rate in intact rats. A reduction in dosage during Period II diminished this acceleration to 3% which was not found to be significant. It is of interest to note that cortisone administration in intact rats produced increases of similar magnitude in both the mandibular and maxillary incisors during each period, whereas hypophysectomy produced a slightly more severe change in the rate of maxillary incisors. The average mandibular rates observed in this experiment are considerably higher than the averages ($2.80 \pm .17$ mm) reported by Sturman (1957) but are very similar to the averages (3.11 mm) reported by Domm and Marzano (1954).

The lengths of maxillary incisors, as measured from the gingival crest and averaged and plotted graphically (Figure 13), showed some rather constant rela-

tionships. There was a small but consistent increase with age in the length of the incisors of normal rats which was closely paralleled by the two cortisone-treated groups up to the seventh week of the experiment. At this time the incisor length of treated hypophysectomized rats showed a decrease, which partially corresponds to the period of reduced dosage and reduced rates. The difference in incisor length between treated and non-treated hypophysectomized rats appeared quite substantial and was substantiated by the measurements on x-rays reported in a later section (Tables VI and VII).

The effects of an increase in the dosage of cortisone following 12 weeks of treatment, or without previous treatment, were studied during Period III, and are summarized in Table III. During this period the increased dosage (1.0 mg) resulted in similar increases in rate in both Groups II and III, regardless of whether there was previous treatment or not. The difference between these two groups was not significant ($F = < 1$), when analyzed by the Analysis of Variance Test. This is interpreted as indicating that following 12 weeks of treatment there was no change in the sensitivity of the incisor to cortisone at the dosage injected. Additional comparisons for this period indicated significant ($P = .001$) differences between the normal controls and each of the other three groups.

6. Food Restriction

Six rats, forty days of age, were housed for three weeks under identical conditions and simultaneously with the 10 normal controls of the preceding experiment. Eruption rates of incisors in both groups were exactly the same

during this period (Figure 14). During the next four weeks these rats were maintained in separate plastic cages, without sawdust, and fed ground Purina Dog Chow instead of pellets. Food and water were provided ad libitum, and the daily food consumption recorded. Cages were cleaned daily. The amount of food provided daily was then gradually decreased until only a little was left at the end of a 24 hour period. During this period the weekly eruption rates of the two groups showed some variation but averages were the same. At the end of the seventh week the amount of food provided was restricted to 25% of that previously consumed and observations continued for another two weeks. The body weights of the starved rats showed an average loss of 46 grams or a 26% reduction when compared with the ad libitum controls by the end of the second week. There was no significant change in eruption rates during this time.

7. Adrenalectomy, Thyroidectomy, Chemical "Thyroidectomy," and Hypophysectomy

In this experiment measurements were made on 18 adrenalectomized rats given drinking water containing 1% sodium chloride and 0.1% 6-n-propylthiouracil, on 14 adrenalectomized given 1% NaCl, 13 hypophysectomized, 12 normal controls, 18 intact rats given 0.1% 6-n-propylthiouracil in the drinking water, and 18 thyroidectomized rats. The operations were performed at 40 days of age, observations beginning on the day following the operation. The experiment terminated 12 weeks later. The consumption of water containing thiouracil was recorded daily in order to evaluate the amount of drug consumed. In addition, 6 rats, adrenalectomized at 40 days of age, received daily injections of a 0.5% solution of 6-n-propylthiouracil, at a dose of 50 mg per kilogram, and

were maintained on 1% NaCl. This last group was started during the third week of the experiment. At the termination of the experiment, six of the thiouracil-treated intact rats were continued on the same treatment for an additional eight weeks. Four of the animals received daily injections of 1.5 mg cortisone, the remaining two serving as controls.

The effects of removal of the various endocrine glands on eruption rate are summarized in Tables IV and V and shown graphically in Figure 15. Adrenalectomy resulted in a 26% reduction at one week following the operation, which was not quite so severe as the reduction observed following thyroidectomy (34%) for the same period of time, a difference which proved to be significant ($P = .05$). Thiouracil treatment, during this first week, did not result in so severe a reduction as was observed following thyroidectomy ($P = .001$), but did produce a significant (11%) decrease when compared with normal controls, indicating that a chemical "thyroidectomy" had at least been initiated during this first week. When adrenalectomized rats were fed 0.1% thiouracil in addition to NaCl in the drinking water, eruption rates became severely depressed to a level slightly below that observed in the same length of time following hypophysectomy. This difference was not statistically significant. All the animals succumbed on about the sixth day (average 6.4 days).

The reduction in rate observed following thyroidectomy, when added to that produced by adrenalectomy, was 60%, which was slightly more than the 53% reduction observed in our hypophysectomized rats. The sum of the squares of the thyroidectomized and adrenalectomized groups were combined and compared with the total sum of the squares of the normal and hypophysectomized groups,

and the "between group mean square" compared with the "within group mean square" or error. This comparison proved not to be significant, which was interpreted to indicate that the effects of each operation were additive and equaled the effects of hypophysectomy. A similar comparison, utilizing the data for the first six weeks, gave the same results.

A similar analysis was made combining the thiouracil-treated intact group with the adrenalectomized group in comparison with the combination of normal and thiouracil-treated adrenalectomized groups. The sum of the reductions in the former grouping was 37% (11% plus 26%) as compared with a 56% reduction, resulting from the combined treatment (adrenalectomy plus thiouracil). This difference was found to be very significant ($P = .01$), indicating that the adrenalectomized rats were more sensitive to thiouracil treatment than the intact rats.

The eruption rates of adrenalectomized rats, observed in two previous experiments when the animals were dying of adrenal insufficiency, are included in Table IV for purposes of comparison. Inspection of the table will show that the rates observed at this time do not approximate those observed in the hypophysectomized or thiouracil-treated, adrenalectomized rats. They appear to approximate more closely the rates observed in the thyroidectomized as well as in the adrenalectomized animals. This suggests that the severity of reduction produced by thiouracil treatment in adrenalectomized rats cannot be ascribed to the moribund condition of the rats at the time of measurements.

The eruption rates of six thyroidectomized rats, found to be complete by histological examination of the thyroid area and the retardation in weekly

weight gains, showed a more severe reduction during the 12 weeks of measurement than did the adrenalectomized rats ($P = .01$, Figure 15). This reduction was also more severe ($P = .001$) than that observed in thyroidectomized rats possessing demonstrable thyroid rests or in those in which weekly weight gains were not so severely retarded. The average rate of completely thyroidectomized rats for the first six-week period was 1.54 mm (39% reduction). During the following six weeks rates showed a further reduction averaging 1.17 mm (54% reduction). The difference between the averages for the two periods was significant ($P = .001$) as determined by the t-test. The averages for incompletely thyroidectomized animals, although not so severe as those of completely operated ones showed reductions of 27% and 31%, which were more severe than those observed in Experiment 3, following thyroidectomy in young adults (20% reduction).

Thiouracil treatment produced a reduction in rate by the end of the third week of treatment which closely approximated the reduction produced by surgical removal of the thyroid. Differences in rate were significant ($P = .05$) for the first six-week period, but not for the second, probably as a result of a delay before a complete "block" of the thyroid was established during the first period.

The body weights (Figure 16) of thiouracil-treated rats showed an almost complete cessation in weekly gains and were slightly below those of the thyroidectomized group. It is of interest to note that the hypophysectomized rats showed a small but consistent weight gain of approximately two grams per week and had almost attained the same weight as the thiouracil-treated rats by the

end of the experiment. The eruption rates of the hypophysectomized rats, however, at that time were approximately one-half those of the thiouracil-treated and the thyroidectomized rats.

The water consumption of thiouracil-treated rats consistently averaged approximately 10 cc, or 10 mg of thiouracil, per day throughout the experiment. Calculated on the basis of body weight the dosage averaged approximately 77 mg per kilogram of body weight which is more than the minimum effective dosage according to Astwood, Bissell and Hughes (1945) and probably accounts for the complete cessation of growth.

Adrenalectomy resulted in a somewhat higher mortality rate in this experiment than in the previous one. Seven of the fourteen animals died by the fourth week, post-operatively, despite free access to drinking water containing 1% NaCl. Two of the remaining seven possessed adrenal rests at autopsy and the data on these were therefore not included in our calculations. The average eruption rate for the first six weeks showed a reduction of 29% which was similar to that observed in the previous experiments. This reduction tended to become less severe during the second six-week period and averaged only 15% below normal. Both averages proved to be significantly different from the averages of normal controls.

The daily injection of thiouracil at a dosage of 50 mg per kilogram of body weight resulted in a better tolerance to the drug as evidenced by the longer survival period (four to eight weeks) and the increase in weight during the first four weeks of treatment. This may have been due to an incomplete blockage of the thyroid since McGinty et al (1948) reported a partial resump-

tion in radioactive iodine uptake in rat thyroids, eight hours following a single injection of 6-n-propylthiouracil. The effectiveness of treatment was not ascertained in the present experiment, however, eruption rates of thiouracil-treated adrenalectomized rats were reduced to approximately the same degree as those observed in hypophysectomized rats. The average rate (1.17 mm) for eight weeks of treatment coincided almost exactly with the average (1.14 mm) of hypophysectomized rats for approximately the same period of time.

These observations, and others following thiouracil feeding in adrenalectomized rats, or following the removal of both the adrenals and the thyroids, clearly indicate that eruption of the incisor in the rat is influenced by the secretions of both the adrenal and thyroid glands. The results also indicate that the adrenal and thyroid hormones probably have a synergistic effect on incisor growth rate.

The daily administration of 1.5 mg cortisone in four rats, previously fed thiouracil for 12 weeks and continued on thiouracil feeding during the period of cortisone injection, increased eruption rates to within the normal range (2.50 mm) for a period of three weeks. However, thereafter, despite continued injections, rates decreased, averaging approximately 2.00 mm per week for the remainder of the period. The average eruption rate for the eight-week period was $2.15 \pm .42$ mm as compared with $1.16 \pm .18$ mm for two thiouracil-treated rats.

8. Effect of Unilateral Adrenalectomy and Adrenal Enucleation

A pilot experiment was conducted to determine the effects of adrenal enu-

enucleation, alone, or combined with ovariectomy or thiouracil treatment. The purpose of this experiment was to determine the amount of adrenal necessary to maintain the normal eruption rate of the incisors. Eleven adult females, 150 to 180 days of age, were used. Observations were made initially for one week, at which time five of the rats were given 0.1% 6-n-propylthiouracil in the drinking water, and observations continued for a second week. At the end of the second week the five thiouracil-treated rats and three others were unilaterally adrenalectomized with enucleation of the remaining adrenal. The remaining three rats were similarly treated and in addition were bilaterally ovariectomized. All animals were maintained on 1% NaCl, added to the drinking water, or on drinking water containing 1% NaCl and 0.1% thiouracil, for five weeks, at which time only the saline treatment was discontinued. Observations were then continued for an additional four weeks.

The right adrenal was removed through an abdominal incision. The left adrenal was enucleated by making a small incision in the capsule and gently squeezing the gland with a small forceps. In this manner the contents of the capsule were expressed and removed. Bleeding was minimal. All operations were performed by the author. Ovariectomies, when performed, were done at the time of the adrenalectomy and through the same incision. Since no observations were made on unoperated or other appropriate controls, no statistical analysis, other than calculation of the weekly averages was performed.

The results following unilateral adrenalectomy combined with enucleation of the other adrenal, thiouracil feeding, and bilateral adrenalectomy are summarized in Figure 17. This experiment was initiated as a pilot study to

help clarify previous observations following adrenalectomy in adult rats not reported in this thesis. The functional significance of adrenal rests became a problem when it was discovered at autopsy that many of the adrenalectomized rats had them. Our observations indicated that small masses of adrenal (<10 mg), seemingly devoid of any medullary tissue, were capable of maintaining eruption rates essentially within the normal range.

The lower range of the normal average eruption rate was considered to be between 2.10 and 2.50 mm (two standard deviations) and any decrease below this was considered as a significant reduction. As seen by inspection of Figure 17, eruption rates showed little change following what appeared to be almost complete removal of all adrenal cortical tissue. The rates for those receiving thiouracil showed a slight reduction which returned to normal when salt maintenance therapy was withheld but thiouracil feeding continued. Since no operated controls were maintained on salt during the last three weeks, conclusions cannot be made as to the effects of the cessation of salt treatment.

These results verified our earlier observations on rats with adrenal rests, since only a small amount of adrenal cortical tissue seemed to be necessary to maintain the normal eruption rate and the presence of the adrenal medulla was apparently not necessary.

B. Roentgenographic Observations

The averages of six measurements, taken from x-ray photographs, are summarized in Table VI, and a summary of the effects of the various experiments on these dimensions is presented in Table VII. Since both incisors of the thyro-adrenalectomized and cortisone-treated thyro-adrenalectomized rats had

been sectioned for histological study before x-ray photographs could be made, these two groups were not included. The t-test was applied only in the evaluation of differences between average measurements of the hypophysectomized and cortisone-treated hypophysectomized rats of Experiment 5. Since the effects of the various treatments, on incisor length, and on the width of the labial dentine, were consistent in all groups measured, it was felt that this was more significant than the application of any statistical analysis in the evaluation of differences between each of the groups.

Measurements on the distance between the fundus of the incisor and the anterior surface of the first molar (Figure 2, Measurement 5) showed the greatest variation of all the conditions studied. This was due to a lack of x-ray definition in the area of the molar socket as well as presumably to normal variations. Initially, during the course of measuring the x-ray photographs of the hypophysectomized and the cortisone-treated hypophysectomized rats of Experiment 5, the distance between the hard palate and the inferior surface of the incisor (Figure 2, Measurement 6) appeared altered, hence this measurement was also made on x-ray photographs of the other animals. However, since this space was apparently affected only slightly, if at all, by the other experimental conditions, only the results of the other four measurements will be discussed in detail.

The width of the labial dentine, at the alveolar crest (Figure 2, Measurement 2), showed a consistent increase following each of the operations. The dentine was thicker following hypophysectomy and appeared to increase in thickness with successively longer post-operative intervals. Adrenalectomy in

young adult rats resulted in an increase in the thickness of the dentine, which was greater than that observed in adult thyroidectomized rats despite the longer post-operative interval following thyroidectomy. However, when these operations were performed on young animals the differences were reversed. Thyroidectomy at 40 days of age resulted in a greater dentine width than did adrenalectomy. The effects of thiouracil feeding on the width of the dentine were essentially the same as those following surgical removal of the thyroid, and were not so great as those observed following removal of the pituitary.

Cortisone administration consistently produced a decrease in the width of the dentine in all groups studied. This was best illustrated in Experiment 5 where the width of the dentine layer of cortisone-treated hypophysectomized rats was less than half that observed in hypophysectomized controls, a highly significant difference ($P = .001$). Reductions of similar magnitude were found in the incisors of young cortisone-treated, thiouracil-fed rats and in adult cortisone-treated adrenalectomized rats. The width of the labial dentine of incisors in the remaining cortisone-treated groups showed similar reductions, although not so great as those previously mentioned.

There appeared to be a constant inverse relationship between the width of the dentine layer and the rate of eruption of the incisor. Removal of the pituitary produced a marked reduction in incisor growth rate and an increase in the width of the dentine layer. Thyroidectomy, thiouracil feeding, and adrenalectomy resulted in reductions in the eruption rate and increases in the dentine width. Conversely, cortisone administration accelerated the eruption

rate but caused a decrease in the width of the dentine in all groups studied.

The width or cross-sectional diameters (Figure 2, Measurement 1) of the incisors of hypophysectomized, thyroidectomized, and thiouracil-fed rats were reduced when compared with those of normal controls. However, adrenalectomy and cortisone administration appeared to have little, if any, effect.

Measurements on the diameter of curvature (Figure 2, Measurement 3) showed similar effects. Hypophysectomy, thyroidectomy, and thiouracil feeding resulted in a decrease, whereas adrenalectomy resulted in an increase in three adult rats, and a decrease in four young rats. Cortisone administration resulted in variable changes in this dimension. The incisors of cortisone-treated hypophysectomized rats showed a significant decrease in the diameter of curvature ($P = .01$) when compared with hypophysectomized controls. The remaining groups showed either no change or a slight increase, following cortisone treatment.

The length of the incisor, as measured from the hard palate (Figure 2, Measurement 4), showed changes consistent with the type of treatment concerned. Endocrine gland removal or thiouracil administration resulted in incisors that were shorter than those of normal controls, whereas cortisone administration produced an increase in the length of the incisors in all groups excepting the intact group of Experiment 3. This increase in length was found to be statistically significant ($P = .01$) when treated hypophysectomized rats were compared with the non-treated hypophysectomized groups in Experiment 5.

III. Histological Observations

Midsagittal sections of the incisors of approximately 100 rats, repre-

senting most of the experimental groups, were examined histologically. Most of the incisors showed the effects of prolonged exposure in the decalcifier as indicated by loss of dentine matrix, basophilia and some loss in the eosinophilia of pulpal tissues. However, the radiographic measurements provided information as to the amount of dentine present. Shorter exposure time in the decalcifier usually resulted in incomplete decalcification of the distal end of the pulp chamber, resulting in tearing and distortion of the tissue during sectioning. A low power view of a sagittal section of an incisor from an hypophysectomized rat is shown in Figure 18 for purposes of orientation. The square delineated in the basal portion of the pulp indicates the area of odontogenic and ameloblastic proliferation and is the area shown at higher magnification in subsequent figures.

Hypophysectomy (8 incisors) resulted in hypoplasia of the enamel organ as evidenced by a reduction in its length and thickness (Figures 20 and 21). The reduction in width appeared to be primarily due to a loss in cellularity of the stratum intermedium and stellate reticulum. However, there appeared to be no change in the ameloblasts (Figures 23 and 24). More distally, in the area of active enamel formation, the ameloblasts presented a normal, tall, columnar appearance. Normally the ameloblasts attain their greatest height over the middle part of the labial surface of the incisor. This is followed by a gradual reduction in the height of the cells as the oral epithelial attachment is approached. Following hypophysectomy, reduction in cell height occurred more proximally, so that the ameloblasts were reduced in height over the middle and distal parts of the incisor. The odontoblasts in the basal

zone appeared to be quite normal. The distal zone was difficult to evaluate due to the irregular arrangement of the odontoblasts in this area.

A study of x-ray photographs (Tables VI and VII) from hypophysectomized rats showed that the dentinal walls were thicker and that there was a reduction in the size of the pulp chamber. There was also a marked decrease in the number and size of the pulpal blood vessels which resulted in a more cellular appearance of the pulp. Normally the pulp of the incisor shows between one and three long, straight, dilated, blood vessels extending from the fundus throughout most of the pulp canal and ending blindly. These in turn give rise, in the basal third of the chamber, to secondary channels (Figures 27 and 28) which often arise at right angles, curving outward toward the odontoblastic layer. The reduction in vascularity following hypophysectomy appeared to be primarily the result of a decrease in the number and size of the secondary channels and their branches.

The administration of 1.5 mg cortisone in hypophysectomized rats produced little if any histological change in the enamel organ (nine rats, Figures 22 and 25) when compared with operated controls (Figures 21 and 24). The reduction in the length and thickness of this structure following hypophysectomy appeared unchanged as a result of cortisone administration. There was also no perceptible change in the height of the mature ameloblasts over the middle and distal surfaces of the incisor. In these areas the ameloblasts were reduced in size and showed no perceptible modifications when compared with the incisors of nontreated hypophysectomized rats.

The pulpal fibroblasts of hypophysectomized rats receiving cortisone

appeared to be smaller and less numerous in some areas, however, this was difficult to ascertain in all cases. The nuclear membrane of these cells appeared slightly thicker and more basophilic, but again this was not consistently observed in all cases. The pulpal blood vessels (Figures 19 and 28) were quite large and prominent, and revealed an increase in the number of dilated secondary channels and their branches. The pulp chamber (Figure 19) was enlarged and extended more distally than was the case in the incisors of hypophysectomized controls (Figure 18). There was no discernable change in the histological appearance of the incisors as the result of a reduction in dosage (0.5 and 0.25 mg) of cortisone (6 incisors, Figure 26) when compared with the effects of the higher (1.5 mg) dosage (Figure 25).

Thyro-adrenalectomy (6 incisors) resulted in changes similar to those observed following hypophysectomy. The enamel organ showed a similar atrophy and the mature ameloblasts were reduced in height over the middle and distal labial aspect of the incisor. The number and size of the secondary channels was reduced when compared with normal controls, but the reduction was not so severe as that noted following hypophysectomy. Similar changes were observed in the incisors of five adult thyroidectomized, six young thyroidectomized and five adult thiouracil-fed rats. The ameloblasts showed a more severe atrophy in the incisors of thiouracil-fed and young thyroidectomized rats and there was a more severe reduction in vascularity. This could be correlated with the more severe decrease in eruption rate observed in these two groups.

The administration of 1.5 mg cortisone in thyro-adrenalectomized, thyroidectomized and thiouracil-fed rats increased the vascularity and the size of the

pulp chamber, similar to that observed in cortisone-treated hypophysectomized rats. The ameloblasts of incisors in six cortisone-treated, thyro-adrenalectomized and five adult thyroidectomized rats showed some indication of stimulation in that tall columnar cells were observed over most of the middle part of the incisor but these became reduced in height over the distal part. This condition was not observed in the incisors of the three cortisone-treated, thiouracil-fed rats examined. The ameloblasts of these incisors showed the same reduction in height as was observed following thiouracil feeding alone. There was little if any discernable effect on the enamel organ in any of these groups when compared with nontreated, operated controls.

With the exception of a moderate increase in vasodilatation, the histological appearance of the incisors of four cortisone-treated, adrenalectomized and fourteen cortisone-treated, intact rats did not differ appreciably from that observed in fifteen normal controls. Adrenalectomy alone appeared to produce little if any change in vascularity. The enamel organ appeared to be normal following each of these experimental manipulations. Ameloblastic hypoplasia occurred over the distal part of the tooth in a manner similar to that seen in normal incisors. Pulpal fibroblasts and odontoblasts similarly appeared to be normal and there was no indication of a specific cellular proliferation in response to cortisone treatment.

An observation concerning the blood vessels of the pulp is worthy of note. The wide, central pulpal vessels of many of the incisors were observed to contain a homogenous "clot-like" material at the distal end of the pulp chamber (Figure 29). This material often appeared more dense and eosinophilic than

similar material occasionally found in vessels outside of the pulp. In many of the incisors the distal end of the vessels was completely filled with this clot-like material and the erythrocytes appeared to be "pushed" into it, or the lumen of the vessels was alternately filled with this amorphous material and the packed erythrocytes. The amount and density of this material appeared to decrease following the various endocrine removals and to show a slight increase following cortisone administration (Figures 30 and 31). While it is probably that this clot-like material is related to blood stasis and the slow penetration of fixatives the difference in the density of the material as compared with that observed in other tissues would seem to indicate the need for additional study.

Dentine formation in the proximal portion of the incisor appeared to be disturbed in approximately 16 incisors. This condition was usually characterized by the inclusion of a strip or an irregular accumulation of predentine and dentine within the pulp cavity close to the proliferating odontogenic base (Figures 32 and 33). In some instances it resembled an infolding of the predentine (Figure 32) while in others it appeared as a long strip of predentine and dentine extending down into the pulp along the base of the incisor, at right angles to the long axis of the tooth. Frequently these inclusions were accompanied by seemingly normal odontoblasts (Figures 32 and 33). This condition was noted in the incisors of three cortisone-treated intact and several rats in each of the other treated groups. In the majority of instances the condition was localized.

DISCUSSION

The results of these experiments clearly indicate that the adrenal cortical hormones exert a significant influence on the rate of eruption of the rat incisor and must be considered in the formulation of any hormonal theory to account for the regulation of tooth eruption. The reductions in rate of eruption observed following removal of the adrenals were consistently about the same in each of the four experiments (28%, 25%, 33% and 29%) and appeared to be unaffected by salt maintenance treatment. The reductions in rate observed following thyroidectomy confirm the findings of Baume, Becks and Evans (1954a) and Garren and Greep (1955). However, our results indicate that in young rats this reduction increases in severity when observed for a sufficient period of time. This finding had not been previously reported and is significant in that it paralleled the progressive severity of reductions in rate observed following hypophysectomy.

When the two operations were combined, or chemical "thyroidectomy" was superimposed on adrenalectomy, the combined effects on rate of eruption were additive and equaled in magnitude the effects on rate observed following hypophysectomy. The normal eruption rate would thus appear to be dependent primarily on a synergistic action between the thyroid and adrenal hormones. This does not exclude the possibility of a supplementary action by the somatotropic or the sex hormones. However, the major hormonal influence or control of the eruption rate appears to be that exerted by the thyroids and the adre-

nals.

The histological observations have consistently failed to reveal significant cell hyperplasia following cortisone-induced increases in rate of eruption. On the other hand there was also no indication of any cellular disturbance to account for the pronounced reductions in eruption rate observed following the various endocrine removals. A review of previous experiments by others reveals some interesting observations.

Baume, Becks and Evans (1954c) studied the effects of thyroxin and growth hormone administration in hypophysectomized rats, beginning either at early or later intervals following the operation, and continuing for long intervals. Hypophysectomies were performed at 26 days of age and the animals sacrificed at 306 to 524 days of age. The administration of growth hormone produced an increase in tooth size (incisor thickness and radius of curvature) increased mitotic activity in pulpal connective tissue, increased vascularity, and produced an improvement in dentinogenesis and amelogenesis as compared with hypophysectomized controls. All of the histological changes were accompanied by a singular lack of stimulation in eruption rate. Thyroxin administration on the other hand brought about an increase in eruption rate as well as an increase in incisor dimensions. The combined administration of both hormones resulted in a histological restoration of the incisor tissues and an increase in eruption rate of the same magnitude as that produced by thyroxin alone. The authors concluded that growth hormone had a stimulating effect on the mesenchymal derivatives, the alveolar bone, odontogenic epithelium, and the pulpal connective tissue, thereby enlarging the incisor. Thyroxin had a dif-

ferential effect since it stimulated amelogenesis and eruption but not osteogenesis. Eruption was defined as a basic process of cell proliferation, governed by growth hormone which became effective only through the thyroxin-induced, differential growth of the incisor and periodontal tissues.

If tissue proliferation provided the basic force for the eruptive process then why has the administration of growth hormone so consistently failed to restore the normal eruption rate? Baume et al (1954c) observed that growth hormone stimulated growth of the alveolar bone and the incisor and postulated that the resulting growth of the incisor was "invested continuously into the stimulated alveolar bone." Thyroxin was believed to stimulate only the incisor (differential effect), while the alveolar bone (incisor socket) remained unchanged. They infer from this that thyroxin induces a constriction or compression of the incisor by increasing its diameter without changing the diameter of the socket, and that this compression forces the tooth to erupt. The forces causing the incisor to erupt would thus appear to be similar to those responsible for the ejection of toothpaste when the tube containing it is squeezed. This hypothesis was shown to be invalid by Massler and Schour (1941) and does not explain the normal eruption of the incisors in adult rats, in which the dimensions of the socket and incisor show little change.

The observations in the present experiments further contradict this theory. The administration of 0.5 and 0.25 mg cortisone in hypophysectomized rats resulted in a decrease in the diameter of curvature and no change in the diameter of the tooth. There was no indication in our x-ray photographs of a decrease in the size of the socket, however, as in the study of Baume et al

(1954c), this was not measured. Histologically, the atrophy noted in the enamel organ, following hypophysectomy, showed no indications of a restoration or stimulation following cortisone treatment. Similarly, there was no indication of hyperplasia in either the pulpal tissues or the odontogenic epithelium following cortisone administration.

It should be noted that the incisors, studied by Baume et al (1954c), were from hypophysectomized rats, sacrificed at long intervals following the operation and at a time when the odontogenic and enamel epithelium showed the most severe atrophy. The post-operative interval in the present experiments was between 10 and 19 weeks, a period when according to Baume et al (1954b) and Becks et al (1946) atrophic changes are not yet so severe. Becks et al (1946), after studying the effects of hypophysectomy over progressively longer periods, concluded that the only constant and pathognomonic symptom observed was a thickening of the labial and lingual dentine layers. It is during the initial post-operative period that eruption rates in hypophysectomized rats reveal the severest reduction. The rate of eruption would thus appear not to be effected by the regression of the ameloblasts or odontoblasts, since this change occurs only after very long post-operative intervals, whereas reduction in the rate of eruption is very pronounced within a few weeks after hypophysectomy.

Schour and Van Dyke (1932a), in studying the effects of hypophysectomy on the rat incisor, noted that dentine deposition continued at an apparently unaltered rate, resulting in the obliteration of the pulp canal. They postulated that this represented a dissociation of tissue growth and the process of eruption. This theory was further substantiated by Schour and Hoffman (1939a, b)

in observations on dentine formation as revealed in experiments on alizarin red marking. In this study alizarin was administered at regular intervals after which the animals were sacrificed and the incisors studied histologically. The distance between two alizarin lines in the dentine was measured and divided by the number of days intervening between injections. They calculated the average daily rate of dentine apposition as being 16 micra per day, and came to the conclusion that it was not influenced by hypophysectomy. Roentgenographic measurements in the present experiments substantiate this conclusion. Hypophysectomy, adrenalectomy and thyroidectomy resulted in significant decreases of varying degrees in eruption rates and increases in the width of the dentine layer with a resultant reduction in the size of the pulp chamber. Conversely, cortisone administration accelerated the rate of eruption and resulted in a decrease in the width of dentine. In this respect, thyroxin and cortisone appear to have much the same effect. Garren and Greep (1955) reported a similar thinning of the dentine layer with a widening of the pulp chamber in rat incisors following the feeding of desiccated thyroid.

The histological observations in the present series of experiments would seem to substantiate Schour's theory. In these experiments the eruption rates of hypophysectomized and thyro-adrenalectomized rats have been observed to double following cortisone treatment, without any discernable hyperplasia.

If the eruptive force is not derived from cellular proliferation then what is responsible for this process? Massler and Schour (1941) reviewed the various theories of eruption and concluded that the theory, first proposed by Constant (1900), suggesting a direct relationship between the vascularity of

the teeth and their eruption, was the only theory which satisfactorily explained all the available clinical and experimental observations.

Bryer (1957) reported observations which would appear to substantiate this hypothesis. He studied the effects of a variety of experimental procedures on the rate of eruption of the rat mandibular incisor cut out of occlusal contact. When cut out of occlusal contact with its maxillary antagonist, the mandibular incisor revealed a significant increase in rate of eruption. Histologically, a marked increase in vascularity and a decrease in the width of the dentine were noted. Dentinogenesis and amelogenesis appeared to be normal. Bryer also investigated the effects of various dietary deficiencies on this accelerated, unimpeded eruption rate. In each of the experiments where he observed an increase in the eruption rate, he also noted an associated increase in vascularity. When the rates were reduced a reduction in vascularity was observed. In several instances (i.e., fluoride treatment) the increase in eruption rate was accompanied by a severe disturbance in amelogenesis and dentinogenesis. In another series of experiments the incisors were cut out of occlusal contact and the pulp removed. This resulted in a decrease in the rate of eruption. When the same procedure was used in another experiment, and the pulp replaced with gutta-percha, eruption rates showed marked fluctuations for a time and then returned to normal.

Bryer observed that the blood vessels of the incisor are capillaries having a much greater width than that observed in capillary beds elsewhere. These, he postulated, transmit blood pressure directly to the pulpal tissues with the consequent development of a tissue turgor. Since the incisor is a

rigid tube, enclosed in a rigid bony crypt, he concluded that this pressure causes movement of the tooth along the path of least resistance which is the direction in which the incisor normally erupts.

The vasodilatation observed in our histological preparations, in the present experiments, following cortisone administration would appear to support Bryer's hypothesis. However, the nature of the calcification at the distal end of the pulp chamber and its relationship, if any, to the clotting process, observed at the distal end of the central vessels of the pulp, requires further clarification and more attention than it has heretofore received. Bryer's theory of a pressure-induced tissue turgor supplying the main eruptive force is attractive. However, the observed thinning of the dentine concomitant with the vasodilatation and the accelerated eruption rate would lead to the expectation that such an acceleration, if maintained for a sufficient period of time, would produce an incisor composed essentially of a vascular pulp. This has not been observed in any of our experiments following cortisone administration, nor have we noted any gross symptoms of calcification deficiencies, as might be indicated by increased susceptibility to fracturing. The incisor, under the conditions of a continuous cortisone-induced acceleration, has maintained a solid, well calcified appearance and has increased in length as determined radiographically. This suggests that a calcification at the distal end of the pulp chamber may be in progress and of more importance than has heretofore been appreciated. However, this process has eluded analysis by the usual x-ray or histological techniques.

Body weight and food consumption cannot be considered as significant fac-

tors in the regulation of the eruption rate, as indicated by the dietary restriction experiment and by the observations on weight loss in all our experiments following cortisone administration. In this respect cortisone and desiccated thyroid have been reported, by Greenberg and Aterman (1955), to have opposite effects in the rat. The administration of desiccated thyroid stimulated food consumption and increased body weight, whereas the administration of cortisone had the reverse effect.

The occurrence of thyroid rests in thyroidectomized rats in two of our experiments is of interest. The eruption rates in these animals indicated stimulation to varying degrees which was difficult to correlate with the presence of the thyroid tissue. Van Dyke (1953) reported the occurrence of adenoma formation resembling accessory thyroid tissue in the thymus of rats following prolonged thiouracil treatment. Ray, Simpson, Li, Asling, and Evans (1950) used four criteria to determine the completeness of thyroidectomy, performed on a group of 400 newborn rats. Two hundred animals survived the operation and of these only 22 were found to be acceptable as complete thyroidectomies by application of their criteria. Thyroid rests were located either in the isthmus or between the trachea and esophagus. Apparently the occurrence of thyroid remnants, or accessory thyroid tissue, is more common than is generally stated in the literature. It is, of course, conceivable that these occur more frequently when rats are thyroidectomized at an early age than at later ages. Evaluation of the thyroid status of the adult thyroidectomized rats employed in Experiment 3 was difficult. There was no apparent effect on incisor eruption rate or body weight due to the presence or absence of thyroid tissue. The

differences in eruption rate were usually small and inconsistent. In Experiment 7 this problem was circumvented by the addition of a thiouracil-treated group and the use of body weight as a criterion for completeness. The eruption rates of the thiouracil group and the six operated rats, determined as complete, were the same during the second six-week period of observation. The reduction in rate observed at this time was more severe than that observed following thyroidectomy in the young adults.

The difference in reductions in rate of eruption following thyroidectomy in young and adult rats need not necessarily be explained on the basis of thyroid rests. The eruption rates of young animals, possessing thyroid rests at autopsy, often showed more severe reductions than were observed in the adult group. Observations have been reported (Fleischmann, 1951) which indicate that there is a decrease in the thyroxin requirements of older animals. The difference in degree of reductions in rate observed in our two age groups of thyroidectomized rats would seem to provide support for this hypothesis. However, until additional studies are made on the effects of thiouracil on the rate of eruption in young and adult rats this observation cannot be considered conclusive.

The gradual reduction in degree of inhibition of eruption rates observed following adrenalectomy was a consistent and interesting observation. Since this was observed in animals which were known to have been completely adrenalectomized, and which were unable to survive following cessation of maintenance treatment, it can be assumed to have no connection with accessory adrenal tissue. D'Armour and D'Armour (1939) reported a significant increase in the

survival time of adrenalectomized female rats following the administration of gonadotrophins in which there was extensive luteinization of the ovaries. Ovariectomy was observed to abolish the beneficial effects of the gonadotrophin injections. Emery and Greco (1940) reported a similar beneficial effect following the daily injection of progesterone. Since most of the rats used in our studies were females, there is a possibility that the decrease in severity of the reduction in eruption rate, noted at later intervals in females, was the result of ovarian luteinization.

That the incisor is very sensitive to cortisone was indicated by the increases observed in the eruption rate of hypophysectomized and normal rats at daily dosages of 0.5 and 0.25 mg. This dosage is below doses previously administered in our studies on eruption rate and is also below levels reported in experiments by others. Our studies show that the rate of eruption of the incisor can be stimulated for periods up to 12 weeks without any appreciable loss in sensitivity.

SUMMARY AND CONCLUSIONS

1. The effects on the rate of eruption of the maxillary incisor were studied in the rat following hypophysectomy, adrenalectomy, thyroidectomy, thyro-adrenalectomy, and chemical "thyroidectomy," alone, and in combination with cortisone administration. The effects of dietary restriction and of adrenal enucleation were also observed.
2. Complete adrenalectomy consistently resulted in a decrease of approximately 30% in eruption rate. The addition of salt to the drinking water had no significant effect on this reduction during the first week post-operatively. There was no apparent difference in the reductions in rate between immature and sexually mature rats.
3. Thyroidectomy in adult rats brought about a reduction in rate of approximately 20%. In immature rats it resulted in a more severe decrease in rate, which was progressive in nature, averaging 39% and 54% below normal averages for each of two successive six-week periods. Similar reductions were observed following thiouracil administration.
4. When adrenalectomy was superimposed on thyroidectomy in adult rats the effects were cumulative and rates were approximately 50% below normal. Thiouracil, administered in the drinking water of saline-maintained adrenalectomized rats, produced a reduction in rate more severe than that observed in adrenalectomized controls and similar to that observed in hypophysectomized rats. An analysis of the data showed that the sum of the effects

produced by adrenalectomy and by thyroidectomy alone, or by thiouracil treatment combined with adrenalectomy, equaled the effects produced by hypophysectomy. This was confirmed through observations on adrenalectomized rats following injections of a graded dosage of thiouracil. The eruption rates of these animals declined to levels observed in hypophysectomized rats. These observations suggest that the severe reduction noted following hypophysectomy may be due to the loss of the effects of both the adrenal and thyroid hormones. Following the administration of thiouracil adrenalectomized rats revealed a greater decrease in eruption rate than did intact rats, indicating the possibility that removal of the adrenals in the rat increases sensitivity to this drug.

5. Hypophysectomy brought about reductions in rate ranging from 56 to 70%, depending upon the period of observation following the operation. The initial decrease was more severe than that observed following adrenal or thyroid removal and was progressive.
6. Cortisone administration, in daily dosages of 1.5, 0.5, or 0.25 mg, produced significant increases in eruption rate in all groups studied. The highest increase was noted in adrenalectomized rats, followed in order of decreasing responsiveness by intact, thyroidectomized, thyro-adrenalectomized, and hypophysectomized rats.
7. The administration of cortisone in daily dosages of 1.5 and 0.5 mg in hypophysectomized rats restored eruption rates to within the normal range, whereas the administration of 0.25 mg resulted in a lesser but significant response.

8. The restriction of food intake to 25% of that normally consumed over a period of two weeks resulted in a weight loss of 26% but no change in eruption rate. Cortisone administration resulted in a similar, or more severe, reduction in body weight yet the eruption rate was always stimulated. The results indicate that food consumption and body weight have no direct influence on the rate of eruption of the maxillary incisor.
9. The effects of hypophysectomy and cortisone on the eruption rate of mandibular incisors were observed in one experiment. The reductions in rate of mandibular incisors following hypophysectomy were not so severe as those observed in the maxillary incisors of these rats. Rates averaged 41% below normal during the first and 49% during the second six-week period. The administration of 0.5 mg cortisone restored mandibular rates to within the normal range. A reduction in dosage to 0.25 mg resulted in a corresponding reduction in rate.
10. Unilateral adrenalectomy and partial enucleation of the remaining adrenal produced relatively little change in eruption rate as compared with the reductions observed following complete adrenalectomy. These observations confirm those in previous pilot studies with respect to the influence of small adrenal rests in maintaining the normal rate of eruption.
11. Roentgenographic measurements revealed a reduction in the overall dimensions of the incisor and an increase in the width of the labial dentine following hypophysectomy, thyroidectomy, and adrenalectomy. The administration of cortisone in such rats produced a decrease in width of the dentine layer, and an increase in incisor length and variable effects on the

other dimensions of the incisor.

12. Histological examination revealed no demonstrable increase or decrease in the cellular activity of any part of the incisor to account for the increases or decreases in the eruption rates. Although some atrophy of the ameloblasts was noted in the incisors of hypophysectomized, thyroidectomized and thyro-adrenalectomized rats, they showed no clear-cut indication of stimulation following cortisone administration in any of these cases. The most consistent change was an increase or a decrease in the number of dilated blood vessels which in most instances could be correlated with an increase or a decrease in eruption rate. There appeared to be a corresponding increase or decrease in the amount of a clot-like material in the vessels at the distal end of the pulp chamber under these conditions.
13. The results of these experiments are discussed in terms of some of the current theories on tooth eruption. It is concluded that the observations do not substantiate the tissue proliferation theory but that they tend to support the concept that a vascular-induced tissue turgor is primarily responsible for eruption.

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TABLE I

SUMMARY OF THE AVERAGE ERUPTION RATES IN YOUNG MALE RATS
FOLLOWING ADRENALECTOMY AND CORTISONE ADMINISTRATION

Group	Week 1				Week 2				Average Survival in days
	No. Rats	Mn. ¹ in mm	S.D. ² in mm	%	No. Rats	Mn. in mm	S.D. in mm	%	
Normal Controls	6	2.38	.20	100	6	2.35	.34	100	15.0
Adrenalx.	7	1.61	.25	68	-	-	-	-	6.6
Adrenalx. & NaCl	6	1.79	.47	75	4	1.83	.14	78	7.3
Adrenalx. & Cortisone	7	2.88	.18	121	7	2.81	.29	120	15.0
Normals & Cortisone	6	3.09	.15	130	6	2.93	.23	125	15.0

¹Mean.²Standard deviation

TABLE II

SUMMARY OF THE AVERAGE ERUPTION RATES IN ADULT FEMALE RATS FOLLOWING
ADRENALECTOMY, THYRO-PARATHYROIDECTOMY, THYRO-
ADRENALECTOMY AND CORTISONE ADMINISTRATION

Group	Mean	S.D. ¹	No. of Obs.	% of Normal	Complete Thyroidx.	
					Mn.	No. of Obs.
Normal Controls	2.57	.21	30	100	-	-
Intact & Cortisone	2.97	.23	30	116	-	-
Adrenalx.	1.95	.19	26	76	-	-
Adrenalx. & Cortisone	3.16	.36	24	123	-	-
Thyroidx.	2.25	.20	36	88	2.15	18
Thyroidx. & Cortisone	2.89	.24	36	113	2.83	24
Thyro-adrenalx.	1.26	.27	24	49	1.32	12
Thyro-adrenalx. & Cortisone	2.86	.41	30	111	2.87	6

¹Standard deviation.

TABLE III

EFFECTS OF INCREASED DOSAGE OF CORTISONE ON ERUPTION RATES
OF PREVIOUSLY TREATED AND NONTREATED RATS

Group	No. of Rats	No. of Obs.	Previous Treat. Periods I & II in mg	Cont'd. Treat. Period III in mg	Mean	S.D.	% of Normal
I	6	36	No treatment	0.00	2.60	.18	100
II	4	24	No treatment	1.00	2.94	.22	113
III	4	24	0.50 for 6 wks. 0.25 for 6 wks.	1.00	2.92	.22	112
IV	4	24	0.50 for 6 wks. 0.25 for 6 wks.	0.25	2.82	.17	108

TABLE IV

SUMMARY OF AVERAGE ERUPTION RATES IN RATS ONE WEEK FOLLOWING
ADRENALECTOMY, THYROIDECTOMY, THIOURACIL TREATMENT
AND HYPOPHYSECTOMY, IN COMPARISON WITH THE
AVERAGE RATES OF ADRENALECTOMIZED
RATS OF PREVIOUS EXPERIMENTS

Experiment	Group	No. of Rats	Mean	S.D. ¹	% of Normal
7	Normal Controls	12	2.54	.13	100
7	Adrenalx. (NaCl)	12	1.88	.14	74
7	Intact & PTU ² (H ₂ O)	18	2.25	.21	89
7	Thyroidx.	6	1.68	.16	66
7	Adrenalx. & PTU ² (H ₂ O)	16	1.12	.20	44
7	Hypox.	13	1.19	.21	47
1	Adrenalx. ³	7	1.62	.33	74 ⁴
2	Adrenalx. ⁵	7	1.61	.25	68 ⁶

¹Standard deviation.

²0.1% 6-n-propylthiouracil added to drinking water.

³Observed during the seventh week after cessation of salt treatment.

⁴Per cent of normal controls of Experiment 1.

⁵Observed during the first week of the experiment.

⁶Per cent of normal controls of Experiment 2.

TABLE V

SUMMARY OF AVERAGE ERUPTION RATES FOR TWO SIX-WEEK PERIODS FOLLOWING ADRENALECTOMY,
 THYRO-PARATHYROIDECTOMY, THIOURACIL TREATMENT AND HYPOPHYSECTOMY

Group	Weeks 1 to 6					Weeks 7 to 12				
	No. of Rats	No. of Obs.	Mean in mm	S.D. ¹ in mm	% of Norm.	No. of Rats	No. of Obs.	Mean in mm	S.D. ¹ in mm	% of Norm.
Normal Controls	12	72	2.55	.21	100	12	72	2.54	.24	100
Adrenalx.	12-5	47	1.82	.23	71	5	30	2.16	.22	85
Incompl. Thyroidx.	12	72	1.87	.32	73	12	72	1.74	.35	69
Thyroidx.	6	36	1.54	.26	61	6	36	1.17	.17	46
Intact & PTU (H ₂ O)	18	108	1.68	.34	66	18	108	1.23	.25	49
Adrenalx. & PTU (inj.)	8-2	33	1.17	.43	46					
Hypox.	13-9	60	1.14	.24	45	9	45	0.64	.19	25

¹Standard deviation.

TABLE VI

SUMMARY OF ROENTGENOGRAPHIC MEASUREMENTS ON INCISORS FROM DIFFERENT EXPERIMENTS

Exper.	Operation	No. of Rats	Age at Start in days	Cortisone Treatment		Age at Autop. in days	Average Measurements in mm ¹					
				Dose in mg	Duration in weeks		Width of Labial Dentine	Width of Incisor	Diameter of Curvature	Length of Incisor	Distance to First Molar	Hard Palate to Incis. Arch
3	Thyroidx.	6	90	None		244	.68	2.87	7.27	6.27	2.15	2.55
3	Thyroidx.	5	90	1.50	6	244	.51	2.94	7.66	6.50	2.22	2.64
3	Normal Controls	5	90	None		244	.58	2.96	7.66	6.70	2.24	2.76
3	Intact	5	90	1.50	6	244	.52	3.00	7.66	6.72	2.44	2.62
3	Adrenalx.	3	90	1.50	6	244	.53	2.93	7.63	7.23	2.43	2.47
3	Adrenalx.	4	90	None		244	.90	3.03	7.83	6.43	2.48	2.90
4	Normal Controls	8	55	None		167	.63	2.88	7.69	6.38	2.53	2.65
4	Intact	5	55	1.50	7	167	.56	2.98	7.70	6.58	2.54	2.68
5	Hypox.	7	40	None		112	1.03 ²	2.30	6.40	5.09	1.50	2.41
							.13 ²	.18	.23	.20	.15	.12
5	Hypox.	6	40	0.50	6	112	.47	2.35	5.95	5.43	1.43	2.15
				0.25	4		.08 ²	.11	.12	.08	.10	.14
5	Intact	4	40	0.50	6	166	.51	2.85	8.08	6.80	2.00	2.85
				0.25	12							
5	Intact	4	40	0.50	6	166	.53	2.98	7.75	6.70	2.23	2.55
				0.25	6							
				1.00	6							
5	Normal Controls	5	40	None		201	.70	2.94	7.90	7.28	2.28	2.88
6	Normal Controls	12	40	None		124	.58	2.79	7.75	6.28	2.48	2.82
6	Adrenalx.	5	40	None		124	.68	2.74	7.36	5.80	2.24	2.82
6	Hypox.	8	40	None		124	1.16	2.40	6.68	4.76	1.80	2.89
6	Thyroidx.	6	40	None		124	.90	2.62	6.75	5.30	2.00	2.82
6	PTU (H ₂ O)	12	40	None		124	1.00	2.58	6.99	5.34	2.02	2.78
6	PTU (H ₂ O)	2	40	None		180	.95	2.60	7.40	5.40	1.75	3.05
6	PTU (H ₂ O)	4	40	1.50	8	180	.58	2.60	7.18	5.50	1.40	2.90

¹For parts measured see Figure 2.²Standard deviation.

TABLE VII

SUMMARY OF THE EFFECTS OF THE VARIOUS HORMONAL DISTURBANCES
ON ROENTGENOGRAPHIC MEASUREMENTS

Exper.	Experimental ¹ Condition	Width of Labial Dentine	Width of Incisor	Diameter of Curvature	Length of Incisor	Incisor to First Molar	Hard Palate to Incisor
3	Thyroidx.	+	-	-	-	-	0
6	Thyroidx.	+	-	-	-	-	0
6	PTU (H ₂ O)	+	-	-	-	-	0
3	Adrenalex.	+	0	+	-	+	+
6	Adrenalex.	+	0	-	-	-	0
5	Hypox.	+	-	-	-	-	-
6	Hypox.	+	-	-	-	-	0
3	Thyroidx. & Cortisone ²	-	+	+	+	0	+
6	PTU (H ₂ O) & Cortisone ²	-	0	+	+	-	+
3	Adrenalex. & Cortisone ²	-	-	-	+	0	-
5	Hypox. & Cortisone ²	-	0	-	+	0	-
3	Intact & Cortisone	-	0	0	0	+	-
4	Intact & Cortisone	-	+	0	+	0	0
5	Intact & Cortisone ³	-	0	+	+	-	+
5	Intact & Cortisone ⁴	-	0	0	+	-	0

¹In comparison with normal controls of the same age.

²In comparison with operated controls.

³Treated for 18 weeks at a dosage of 0.5, 0.25 and 0.25 mg for each six-week period.

⁴Treated for 18 weeks at a dosage of 0.5, 0.25 and 1.00 mg for each six-week period.

+ = Increase.

- = Decrease.

0 = No change.

TABLE VIII

THE ANALYSIS OF VARIANCE TEST ON ERUPTION RATES OF YOUNG MALE RATS
ONE WEEK FOLLOWING ADRENALECTOMY AND CORTISONE ADMINISTRATION

Source of Variation	df ¹	Sum of Squares	Mean Square	Variance Ratio	p ²
Between Groups	4	11.400	2.850	390.41	.001
Within Groups (Error)	27	1.980	.073		
Totals	31	13.380	-		
Normals vs Adrenalx. & Water	1	1.870	1.870	25.73	.001
Normals vs Adrenalx. & NaCl	1	1.287	1.287	17.63	.001
Adrenalx. & Water vs Adrenalx. & NaCl	1	.037	.037	.51	N.S. ³
Normals vs Adrenalx. & Cortisone	1	.805	.805	11.03	.001
Normals vs Normals & Cortisone	1	1.541	1.541	21.11	.001

¹Degrees of freedom.

²Probability.

³Not significant.

TABLE IX

THE ANALYSIS OF VARIANCE TEST ON ERUPTION RATES OF ADULT FEMALE RATS
FOLLOWING THYRO-PARATHYROIDECTOMY, ADRENALECTOMY
AND THYRO-ADRENALECTOMY

Pe- riod	Source of Variation	df ¹	Sum of Squares	Mean Square	Variance Ratio	p ²
1	Between Groups	1	21.9600	21.9600	181.49	.001
	Within Groups (Error)	390	47.2000	.1210		
	Totals	391	69.1600			
1	Compl. vs Incompl. Thyroidx.	1	1.8000	1.8000	13.78	.001
	Within Groups (Error)	158	20.5800	.1300		
	Totals	159	22.3800			
2	Between Groups	3	77.1600	25.7200	233.82	.001
	Within Groups (Error)	302	32.3200	.1100		
	Totals	305	109.4800			
2	Normal vs Thyroidx.	1	10.2000	10.2000	92.70	.001
2	Normal vs Adrenalx.	1	27.0800	27.0800	246.20	.001
2	Normal vs Thyro-adrenalx.	1	71.3400	71.3400	648.50	.001
2	Thyroidx. vs Adrenalx.	1	5.8200	5.8200	52.90	.001
2	Adrenalx. vs Thyro-adre- nalx.	1	9.1900	9.1900	83.50	.001
2	Normal & Thyro-adrenalx. vs Thyroidx. & Adrenalx.	1	.0014	.0014	< 1	N.S. ³

¹Degrees of freedom.

²Probability.

³Not significant.

TABLE X

THE ANALYSIS OF VARIANCE TEST ON ERUPTION RATES OF ADULT FEMALE RATS FOLLOWING
 THYRO-PARATHYROIDECTOMY, THYRO-ADRENALECTOMY, ADRENALECTOMY
 AND CORTISONE ADMINISTRATION

Source of Variation	df ¹	Sum of Squares	Mean Square	Variance Ratio	P ²
Between Groups	7	73.4400	10.4900	143.70	.001
Within Groups	228	16.5300	.0730		
Totals	235	89.9700			
Adrenalex. & Adr. Rests & Cortisone vs Compl. Adrenalex. & Cortisone	1	0	0	-	N.S. ³
Thyro-Adrx. & Adr. Rests & Cortisone vs Compl. Thyro-adrx. & Cortisone	1	.0001	.0001	-	N.S.
Norm. vs Norm. & Cortisone	1	2.4500	2.4500	33.80	.001
Norm. vs Adrx. & Cortisone	1	4.5600	4.5600	62.90	.001
Norm. vs Thyro-adrx. & Cortisone	1	1.2800	1.2800	17.60	.001
Norm. vs Thyrx. & Cortisone	1	1.6400	1.6400	22.70	.001
Norm. & Cort. vs Adrx. & Cortisone	1	.4400	.4400	6.02	.050
Norm. & Cort. vs Thyro-adrx. & Cort.	1	.1900	.1900	2.60	N.S.
Norm. & Cort. vs Thyrx. & Cortisone	1	.1100	.1100	1.55	N.S.
Thyro-adrx. & Cort. vs Thyrx. & Cort.	1	.0200	.0200	<1	N.S.
Adrx. vs Thyro-adrx.	1	5.9000	5.9000	80.82	.001
Adrx. vs Thyrx.	1	1.4000	1.4000	19.24	.001

¹Degrees of freedom.²Probability.³Not significant.

TABLE XI

SUMMARY OF AUTOPSY OBSERVATIONS 12 WEEKS FOLLOWING
ADRENALECTOMY, THYRO-PARATHYROIDECTOMY,
THIOURACIL ADMINISTRATION AND
HYPOPHYSECTOMY IN YOUNG
FEMALE RATS

Group	No. of Rats	Average Body Weight in gm	Average Thyroid Weight in mg	Average Adrenal Weight in mg
Normal Controls	12	238.0	11.8	51.0
Adrenalex.	5	196.3	15.5	-
Compl. Thyroidx.	6	144.3	-	20.1
Intact & PTU (H ₂ O)	12	134.2	83.9	20.4
Hypox.	8	124.0	¹	10.0

¹Atrophy too severe to permit evaluation.

TABLE XII

INDIVIDUAL INCISOR ERUPTION RATES FOR THE FIRST WEEK IN ADRENALECTOMIZED,
 THYROIDECTOMIZED, THIOURACIL-TREATED AND HYPOPHYSECTOMIZED
 RATS, SUMMARIZED IN TABLE IV

	Groups					
	Normals	Adrenalx.	Thyroidx.	Thiouracil- treated	Adrenalx., Thiouracil-treated	Hypox.
Measurements for First Week	2.44	1.88	1.69	2.50	0.88	1.50
	2.63	1.69	1.81	2.50	1.21	1.25
	2.63	2.00	1.56	2.56	1.21	1.38
	2.63	1.63	1.44	1.88	1.00	1.31
	2.25	2.06	1.69	2.06	1.10	1.00
	2.75	1.81	1.88	2.38	1.21	0.88
	2.50	1.94		2.50	1.10	1.13
	2.63	1.94		2.13	1.21	0.88
	2.56	2.06		2.25	1.48	1.25
	2.56	1.81		2.06	1.21	1.38
	2.50	1.88		2.13	1.10	1.13
	2.44	1.81		1.94	0.97	1.38
				2.38	1.31	0.94
				2.44	0.70	
				2.31	0.88	
				2.25	1.31	
			2.19			
			2.00			
Sum of Obs.	30.52	22.51	10.07	40.46	17.88	15.41
No. of Obs.	12	12	6	18	16	13
Mean	2.54	1.88	1.68	2.25	1.12	1.19
Stand. Deviation	.13	.14	.16	.21	.20	.21

Figure 1. Diagram showing the method employed in measuring the weekly eruption rate of the maxillary incisor in the albino rat.

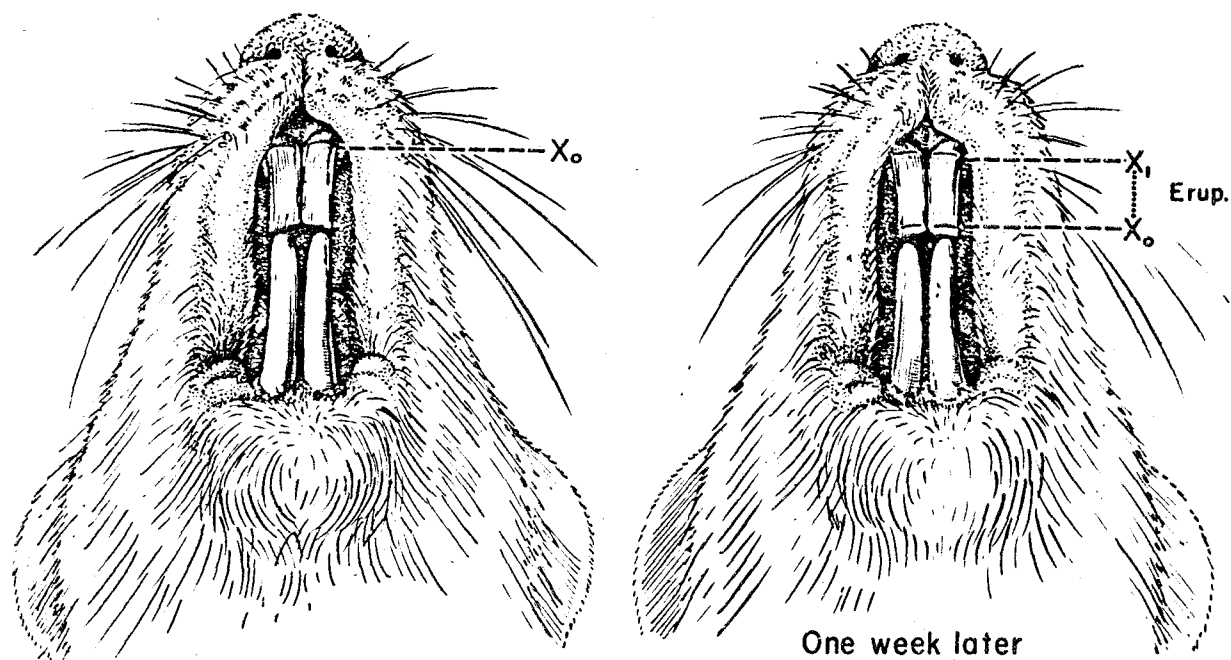


FIGURE 1

Figure 2. Diagram showing the measurements on the rat incisor which were made on x-ray photographs.

- Abbreviations:
- 1 - The width of the incisor at the alveolar crest.
 - 2 - The thickness of the labial dentine at the alveolar crest.
 - 3 - The inside (lingual) diameter of curvature.
 - 4 - The distance between the hard palate and the incisor tip.
 - 5 - The distance between the basal end or fundus of the incisor and the first molar.
 - 6 - The longest distance from the hard palate at an angle of 90° , to the inner surface of the incisor.

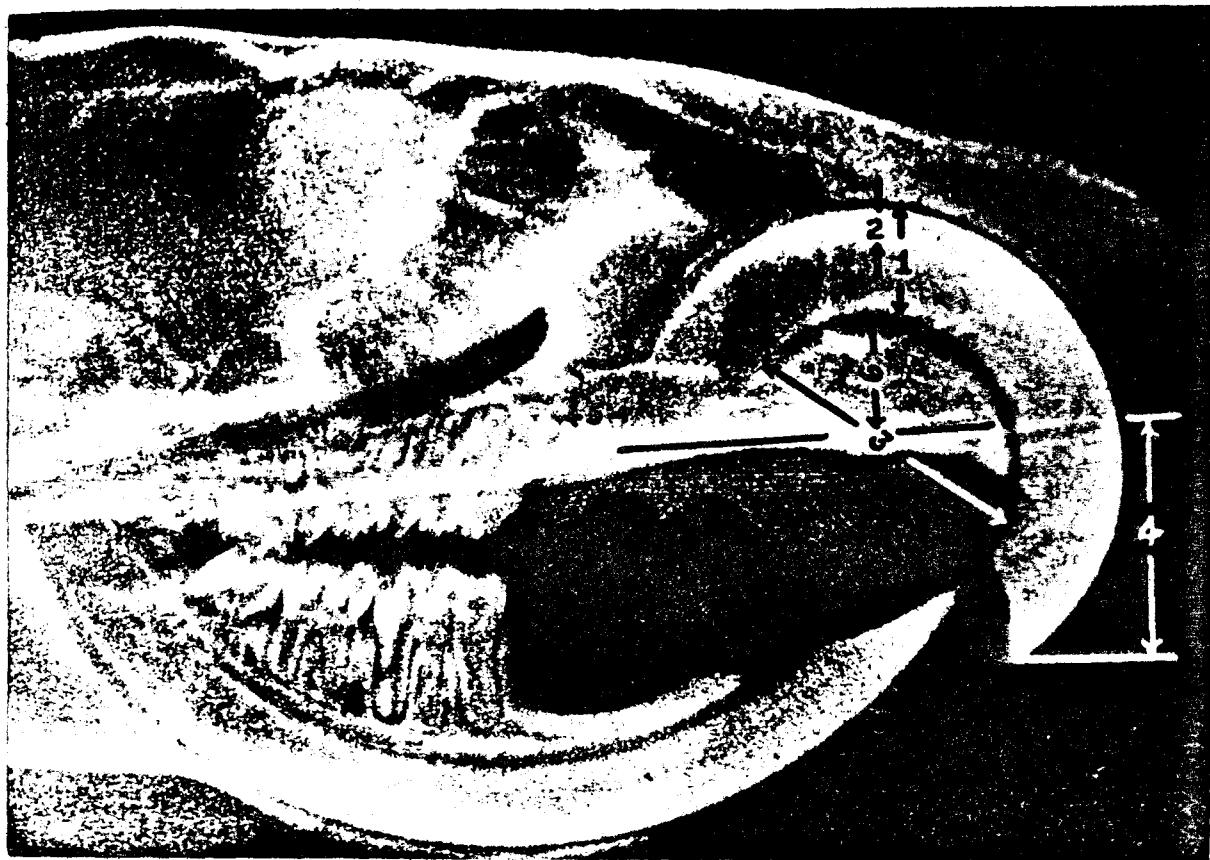


FIGURE 2

Figure 3. The effect of adrenalectomy and cortisone (1.5 mg) on the rate of eruption of maxillary incisors in young female rats.

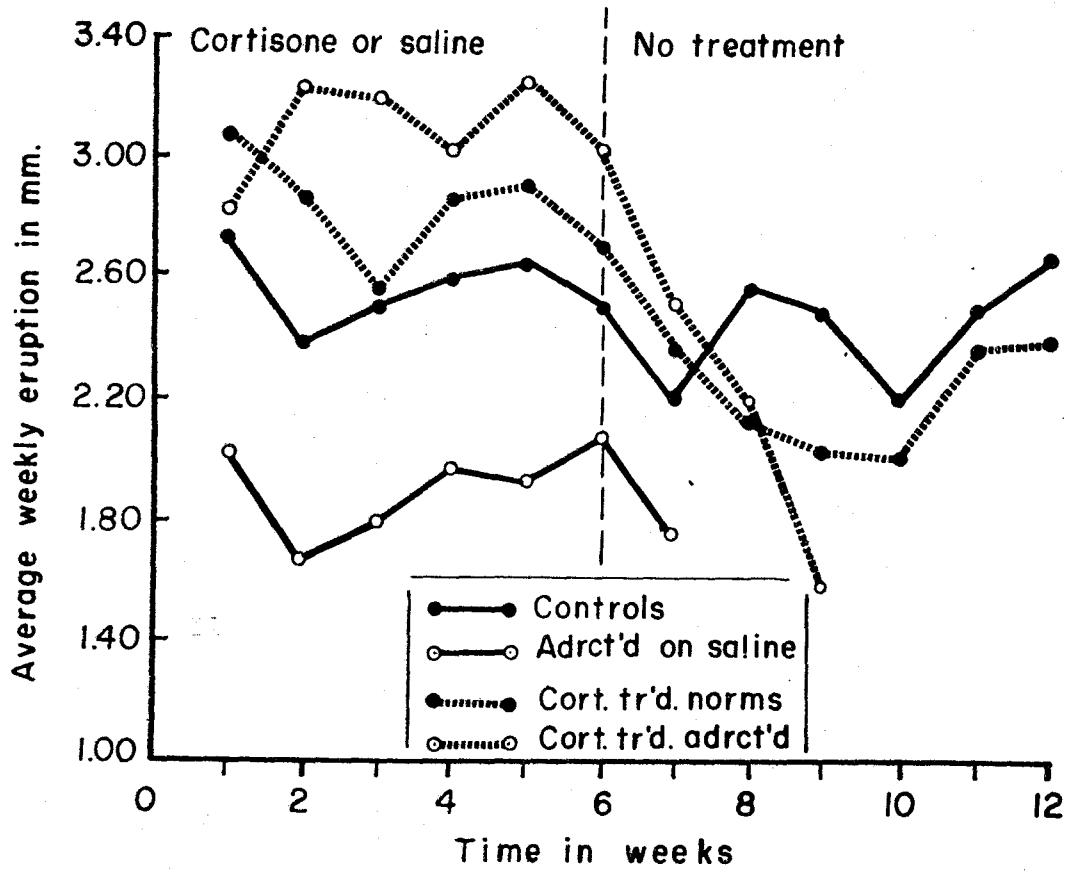


FIGURE 3

Figure 4. The effect of adrenalectomy and cortisone (1.5 mg) on the body weights of young female rats.

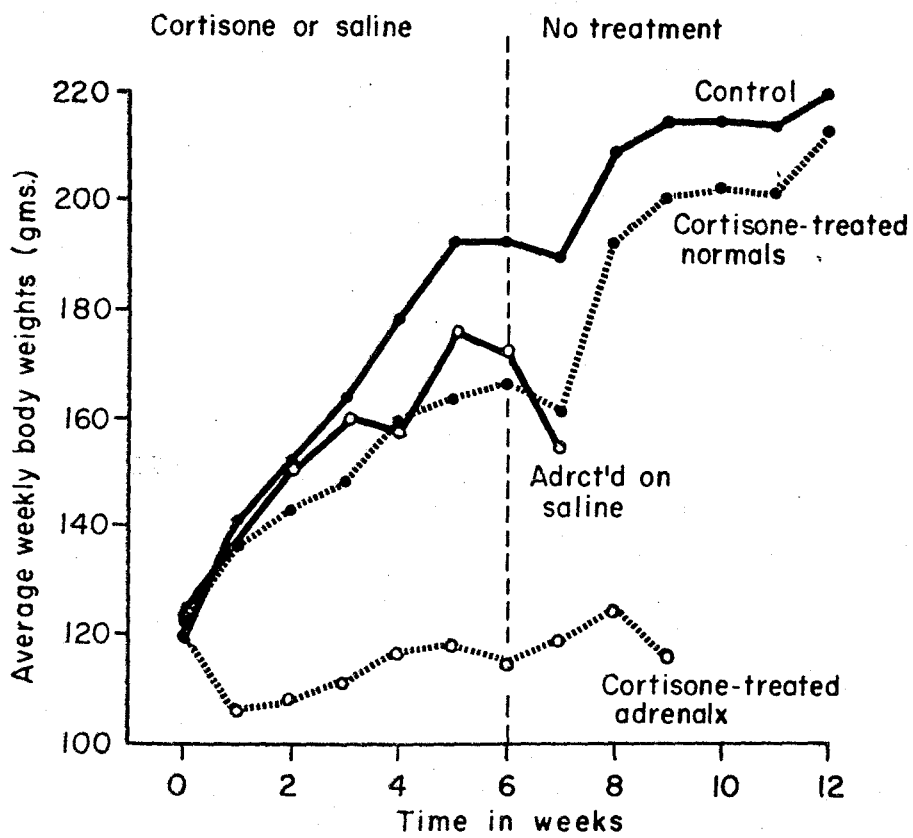


FIGURE 4

Figure 5. The effect of adrenalectomy and cortisone (1.5 mg) on the body weights of young male rats.

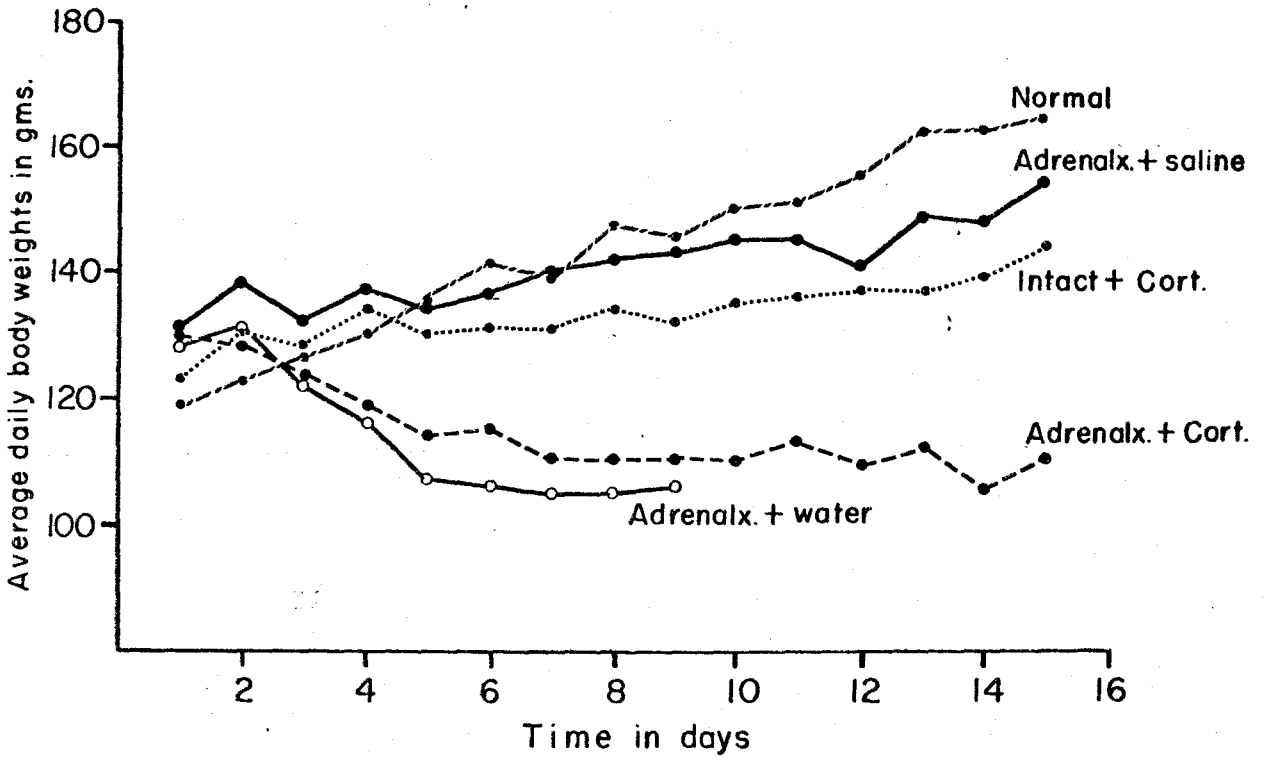


FIGURE 5

Figure 6. The effect of thyroidectomy, adrenalectomy and thyro-adrenalectomy, with (1.5 mg) and without cortisone administration on the rate of eruption of maxillary incisors in young adult female rats. The vertical bars indicate the standard error.

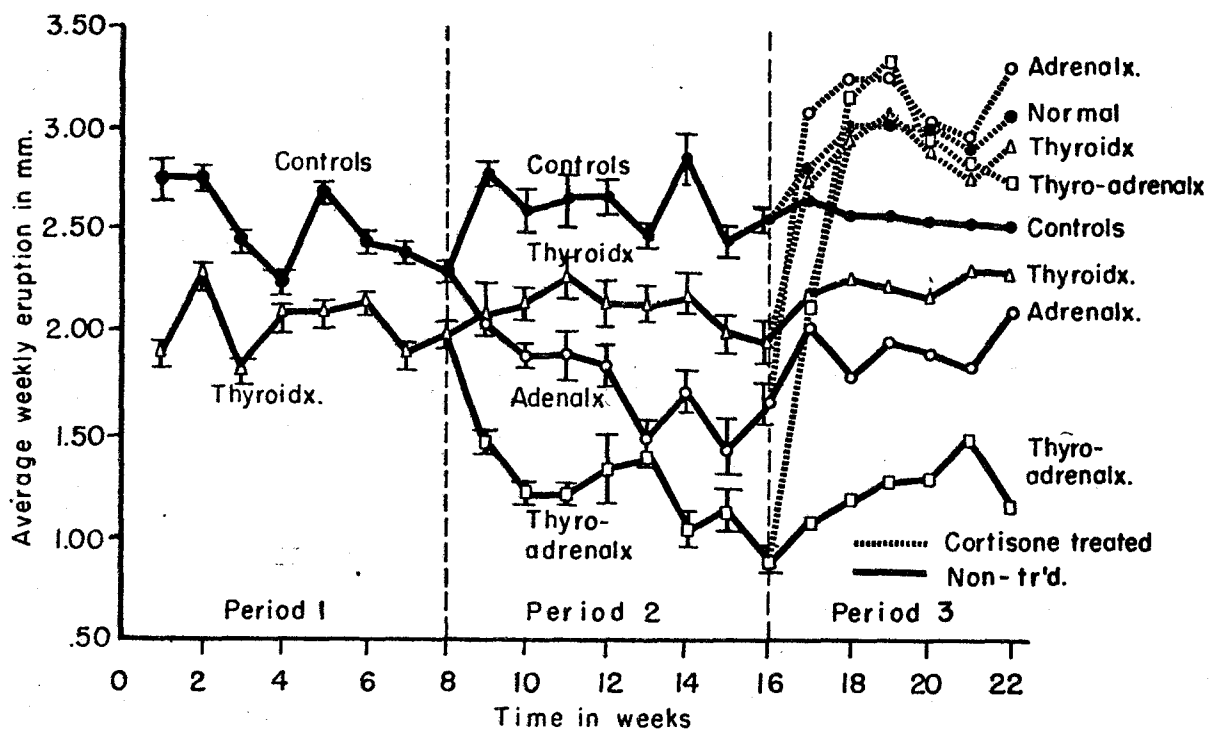


FIGURE 6

Figure 7. The effect of thyroidectomy, adrenalectomy and thyro-adrenalectomy, with (1.5 mg) and without cortisone on the body weights of young adult female rats.

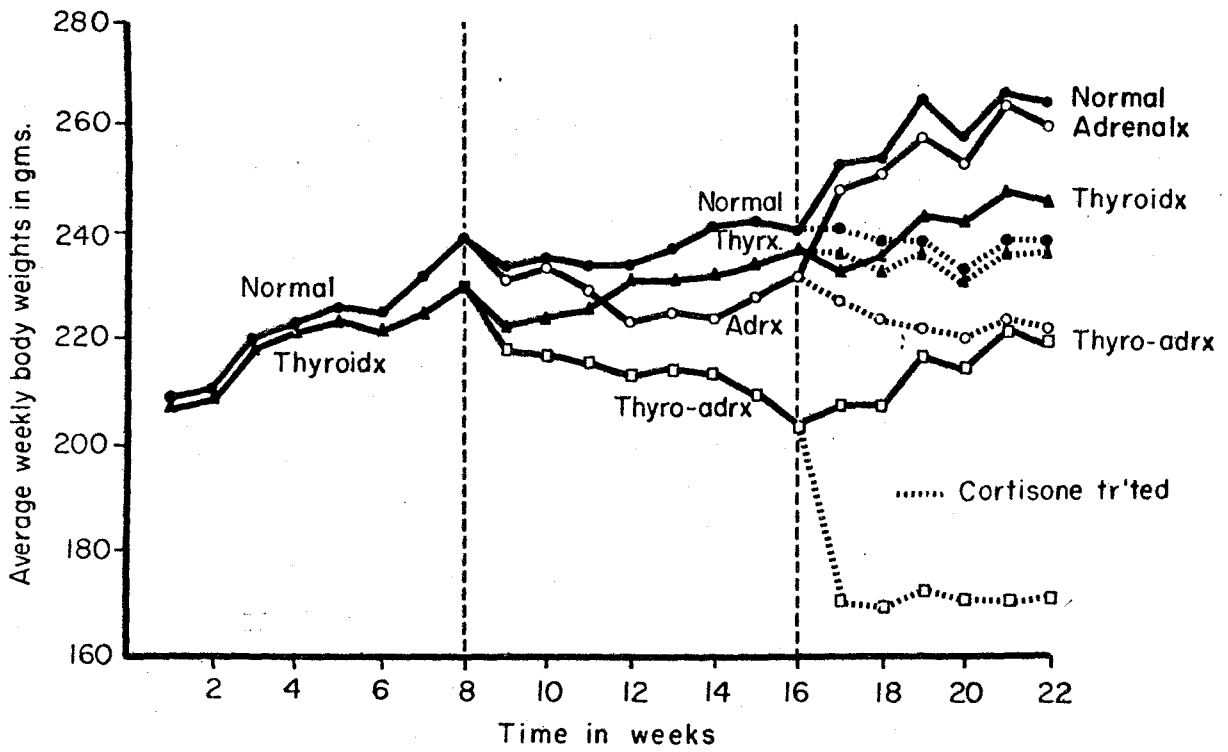


FIGURE 7

Figure 8. The effect of hypophysectomy (age, 26 days) and cortisone (1.5 mg) on the rate of eruption of maxillary incisors in young female rats.

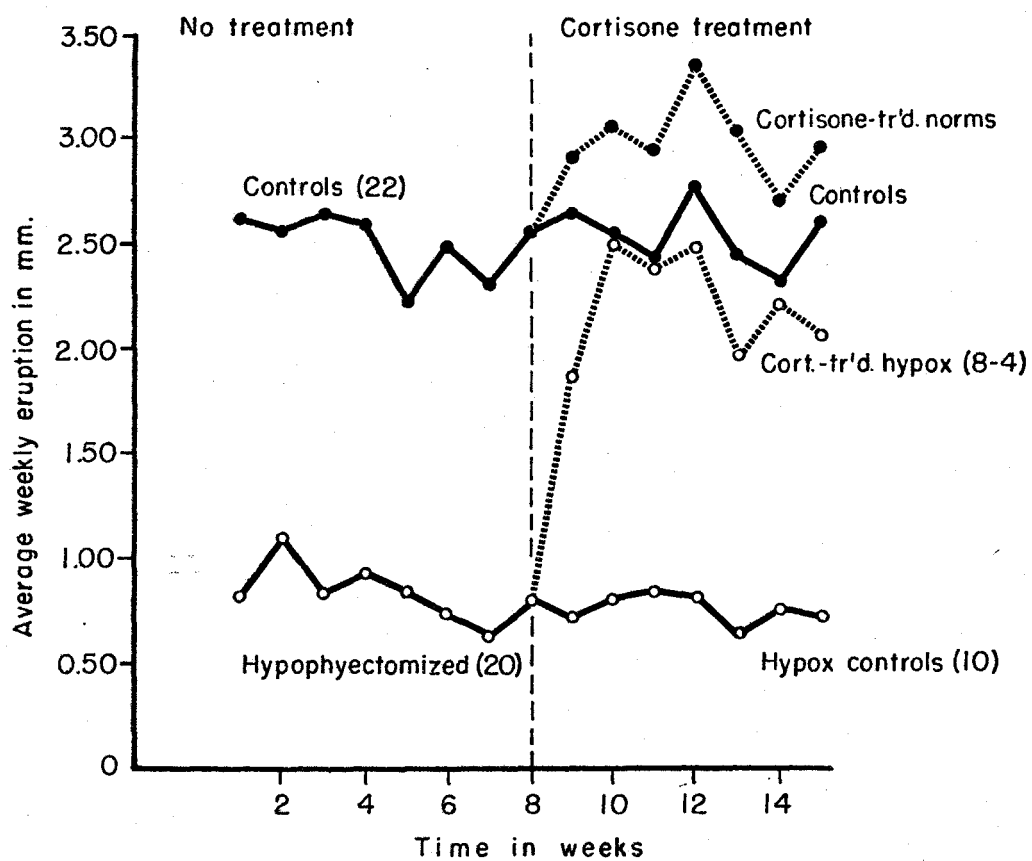


FIGURE 8

Figure 9. The effect of hypophysectomy (age, 26 days) and cortisone (1.5 mg) on the body weights of young female rats.

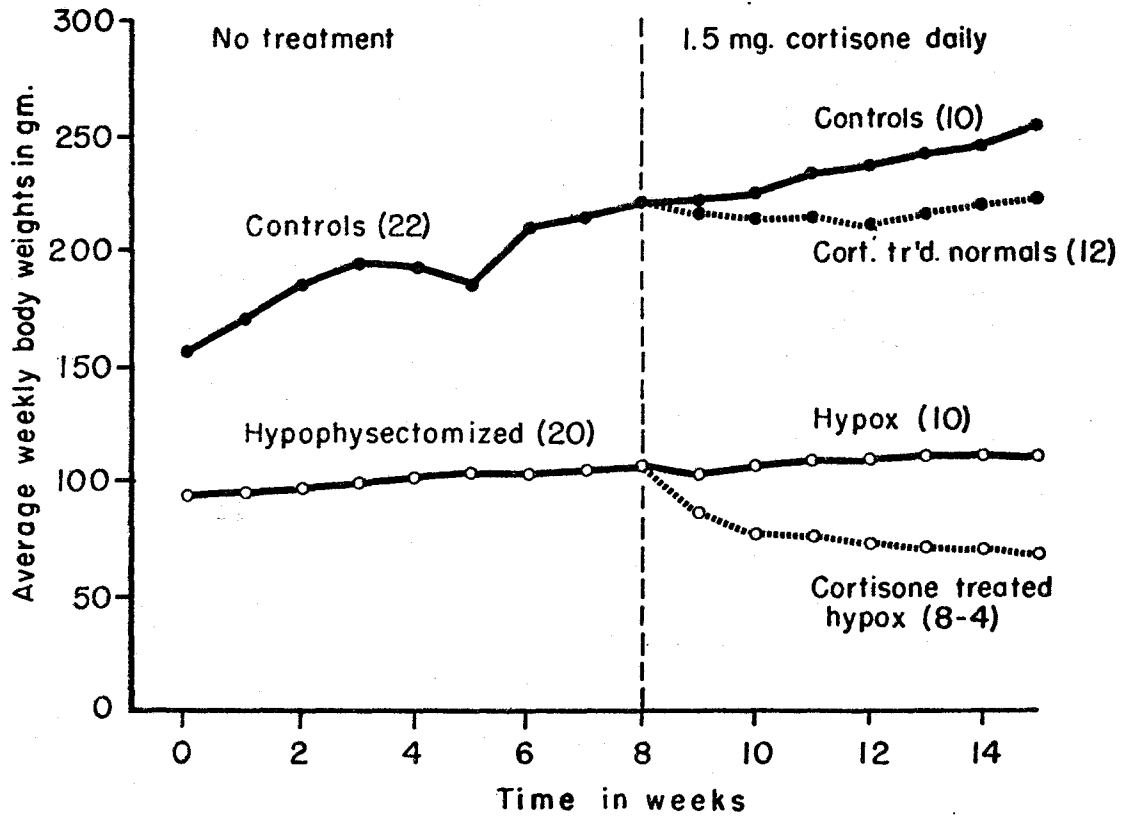


FIGURE 9

Figure 10. The effect of hypophysectomy (age, 40 days) and cortisone (0.5 and 0.25 mg) on the rate of eruption of maxillary incisors in young female rats.

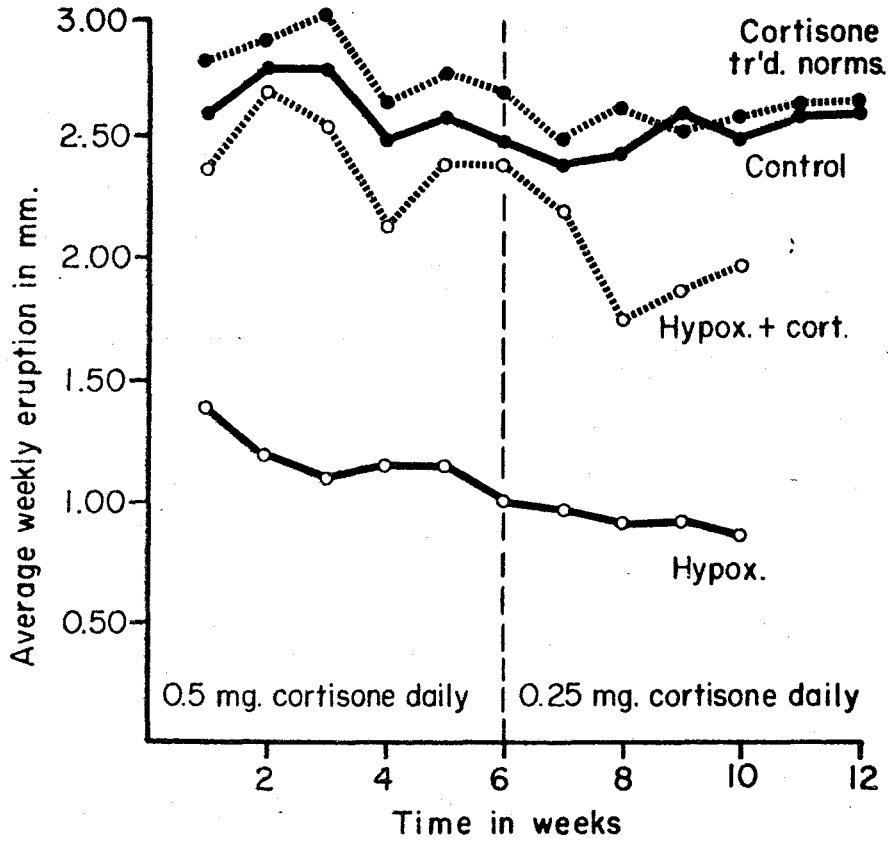


FIGURE 10

Figure 11. The effect of hypophysectomy (age, 40 days) and cortisone (0.5 and 0.25 mg) on the body weights of young female rats.

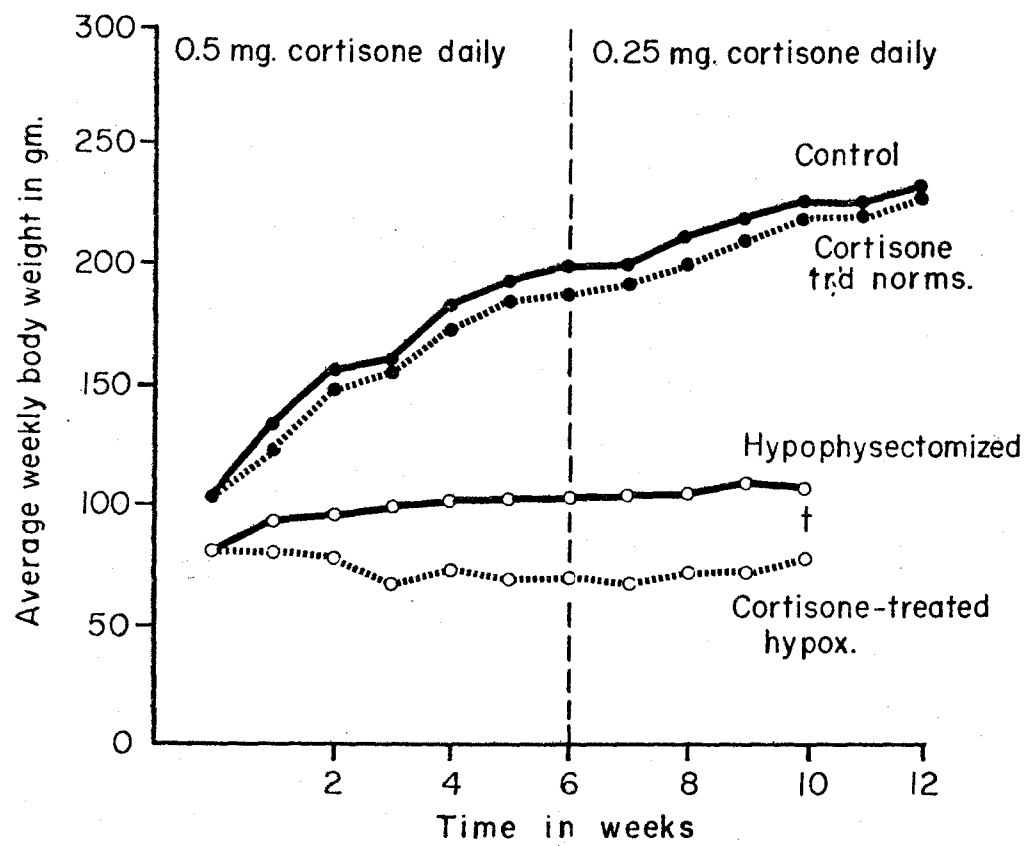


FIGURE 11

Figure 12. The effect of hypophysectomy (age, 40 days) and cortisone (0.5 and 0.25 mg) on the rate of eruption of mandibular incisors in young female rats.

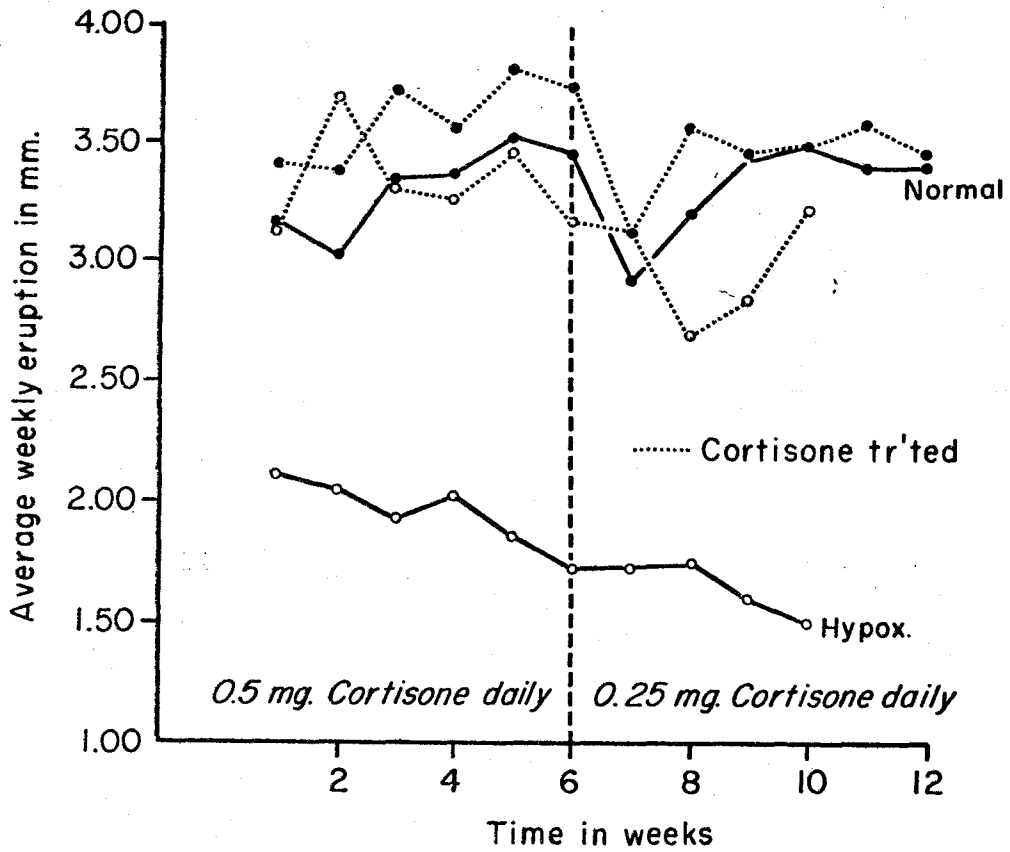


FIGURE 12

Figure 13. The effect of hypophysectomy (age, 40 days) and cortisone (0.5 and 0.25 mg) on the distance from the gingival crest to the tip of maxillary incisors in young female rats.

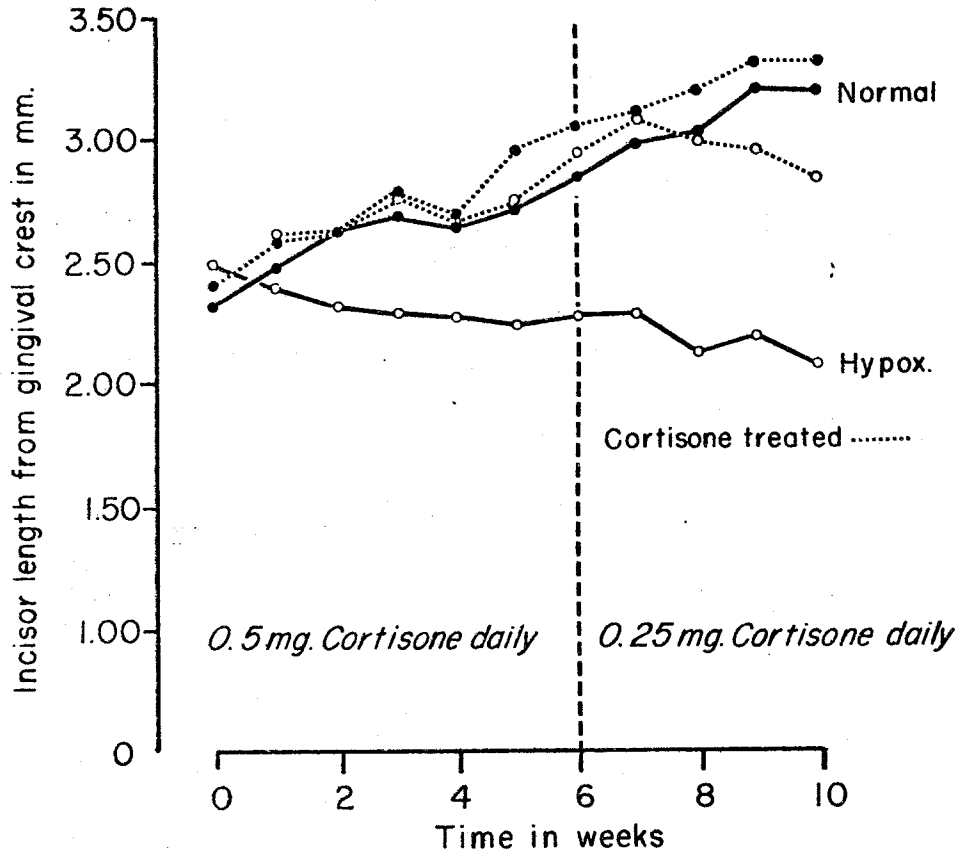


FIGURE 13

Figure 14. The effect of food restriction on body weight and rate of eruption of maxillary incisors in young female rats.

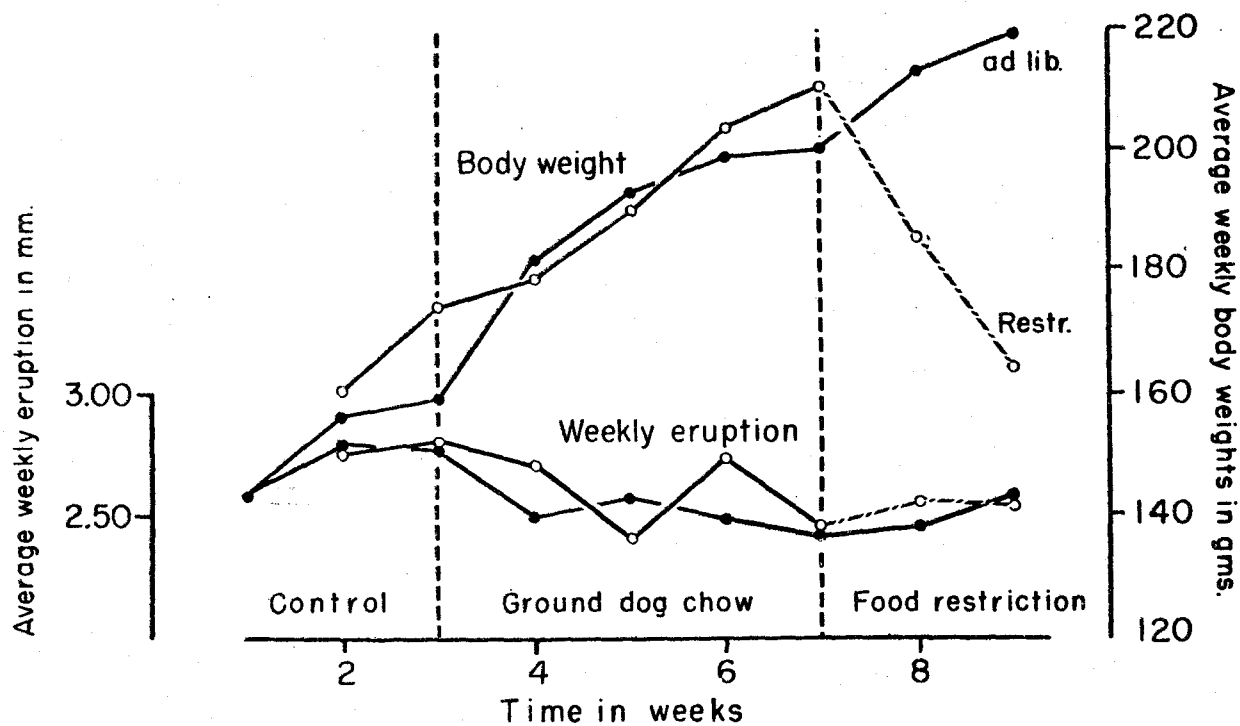


FIGURE 14

Figure 15. The effect of adrenalectomy, thyroidectomy, hypophysectomy, thiouracil administration, and adrenalectomy combined with thiouracil administration on the rate of eruption of maxillary incisors in young female rats.

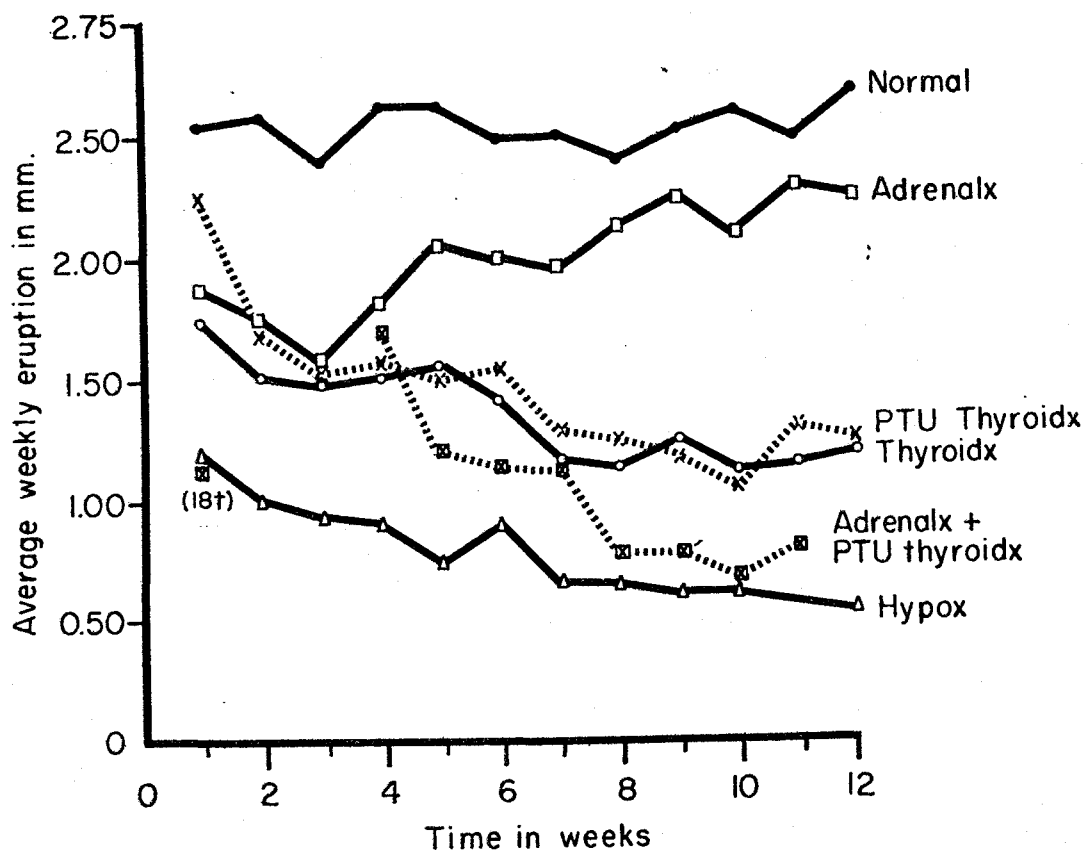


FIGURE 15

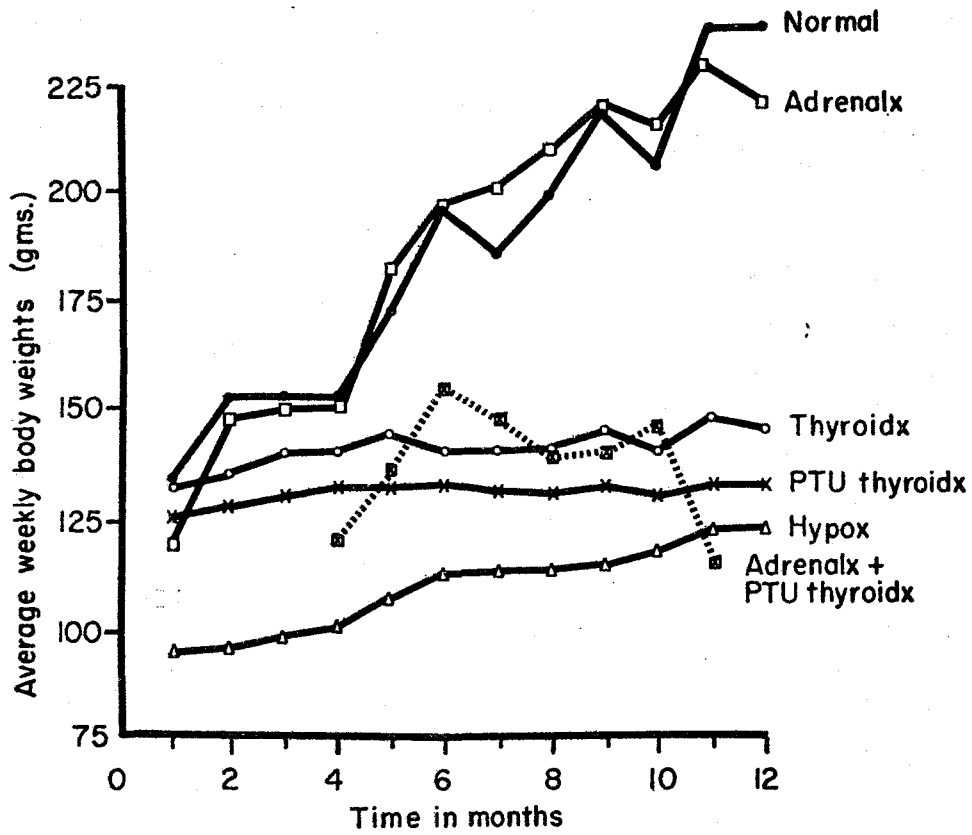


FIGURE 16

Figure 17. The effect of unilateral adrenalectomy with contralateral adrenal enucleation, alone or in combination with bilateral ovariectomy or thiouracil feeding, on the rate of eruption of maxillary incisors in female rats.

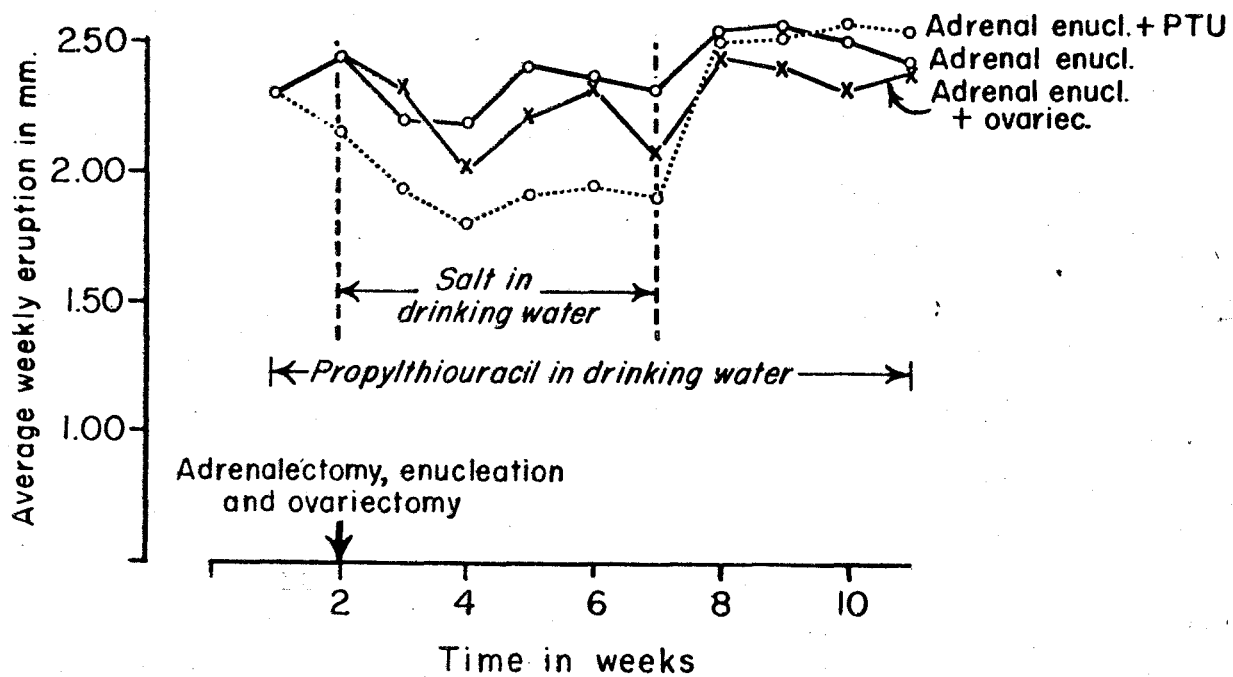


FIGURE 17

PLATE I :

Figure 18. Low power view of a sagittal section of an incisor 19 weeks following hypophysectomy at 26 days of age. The square delineated at the basal portion of the pulp indicates the area shown at higher magnification in subsequent figures. Note enamel space due to loss of enamel as a consequence of decalcification.

Abbreviations: D - Dentine
ES - Enamel Space
P - Pulp



FIGURE 18

PLATE II

Figure 19. Low power view of a sagittal section of an incisor 19 weeks following hypophysectomy at 26 days of age and daily administration of 1.5 mg cortisone for the last seven weeks. Note the increase in vascularity and the decrease in the width of the dentine when compared with Figure 18.

Abbreviations: D - Dentine
ES - Enamel Space
P - Pulp

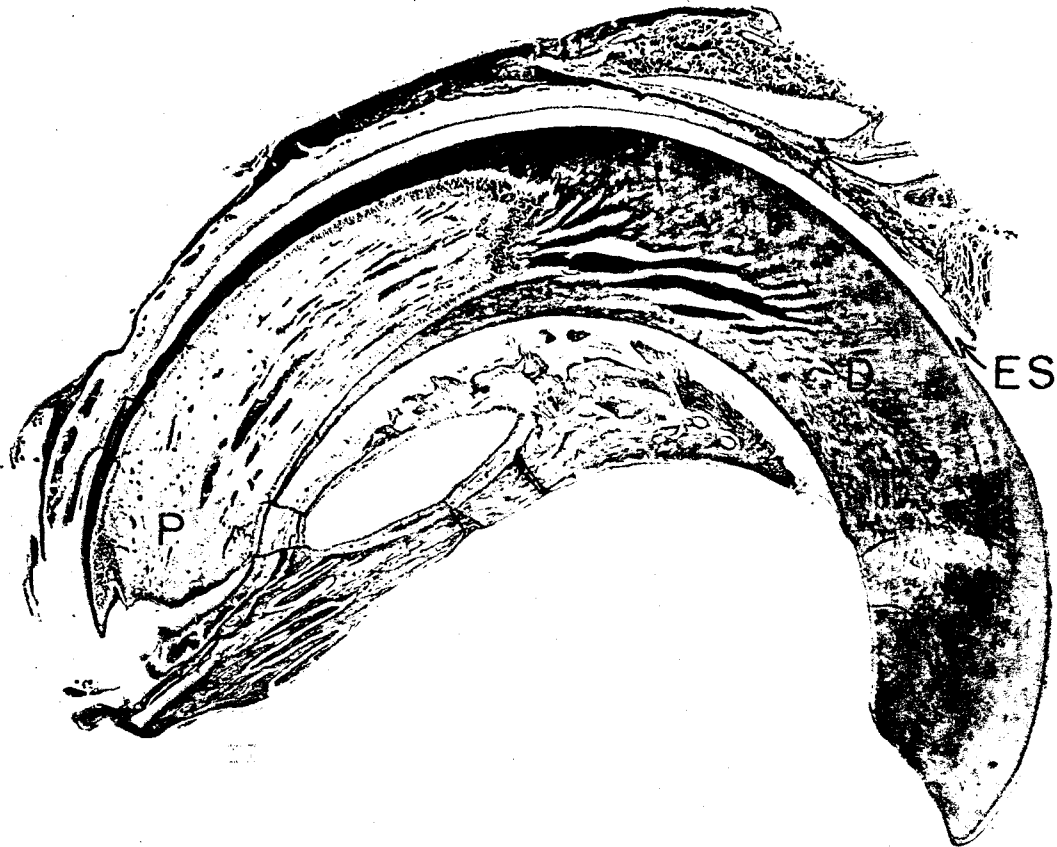


FIGURE 19

PLATE III

Figure 20. Odontoblastic and ameloblastic epithelium from a maxillary incisor of a normal rat. (x150)

Abbreviations: A - Artifact due to shrinkage
Am - Ameloblasts
EO - Enamel Organ
Od - Odontoblasts
P - Pulp
SI - Stratum Intermedium
SR - Stellate Reticulum

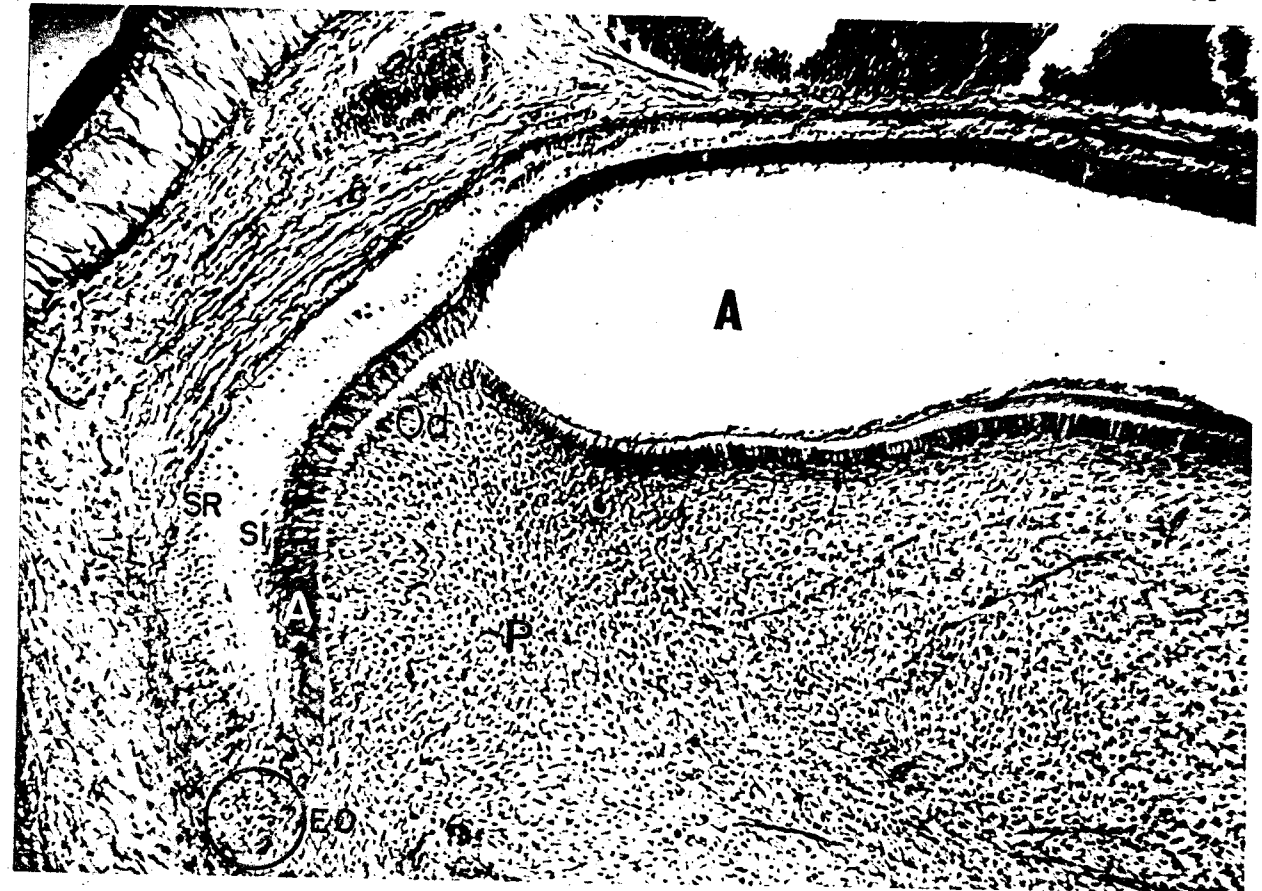


FIGURE 20

PLATE IV

Figure 21. Odontoblastic and ameloblastic epithelium of a maxillary incisor, 19 weeks following hypophysectomy at 26 days of age. Note the reduction in size of the enamel organ when compared with Figure 20. (x150)

Abbreviations: A - Artifact due to shrinkage
Am - Ameloblasts
D - Dentine
EO - Enamel Organ
Od - Odontoblasts
P - Pulp

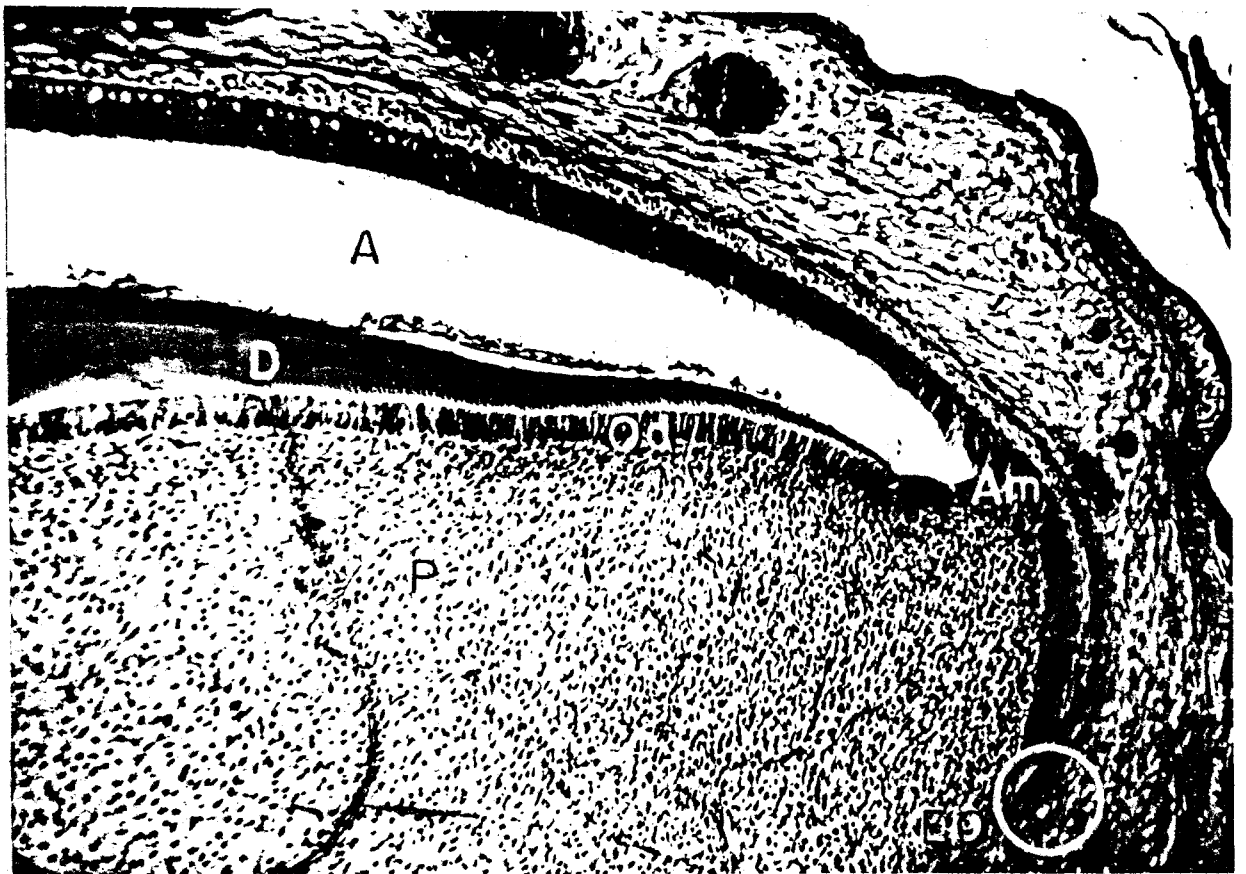


FIGURE 21

PLATE V

Figure 22. Odontoblastic and ameloblastic epithelium of a maxillary incisor, 19 weeks following hypophysectomy at 26 days of age and daily administration of 1.5 mg cortisone for the final seven weeks. Note the apparent lack of tissue stimulation when compared with Figure 21.

Abbreviations: A - Artifact due to shrinkage
Am - Ameloblasts
D - Dentine
EO - Enamel Organ
Od - Odontoblasts
P - Pulp



FIGURE 22

PLATE VI

Figure 23. Odontoblastic and ameloblastic epithelium from a maxillary incisor of a normal rat. (x360)

Abbreviations: Am - Ameloblasts (proliferating)
Od - Odontoblasts (proliferating)
P - Pulp
SI - Stratum Intermedium
SR - Stellate Reticulum

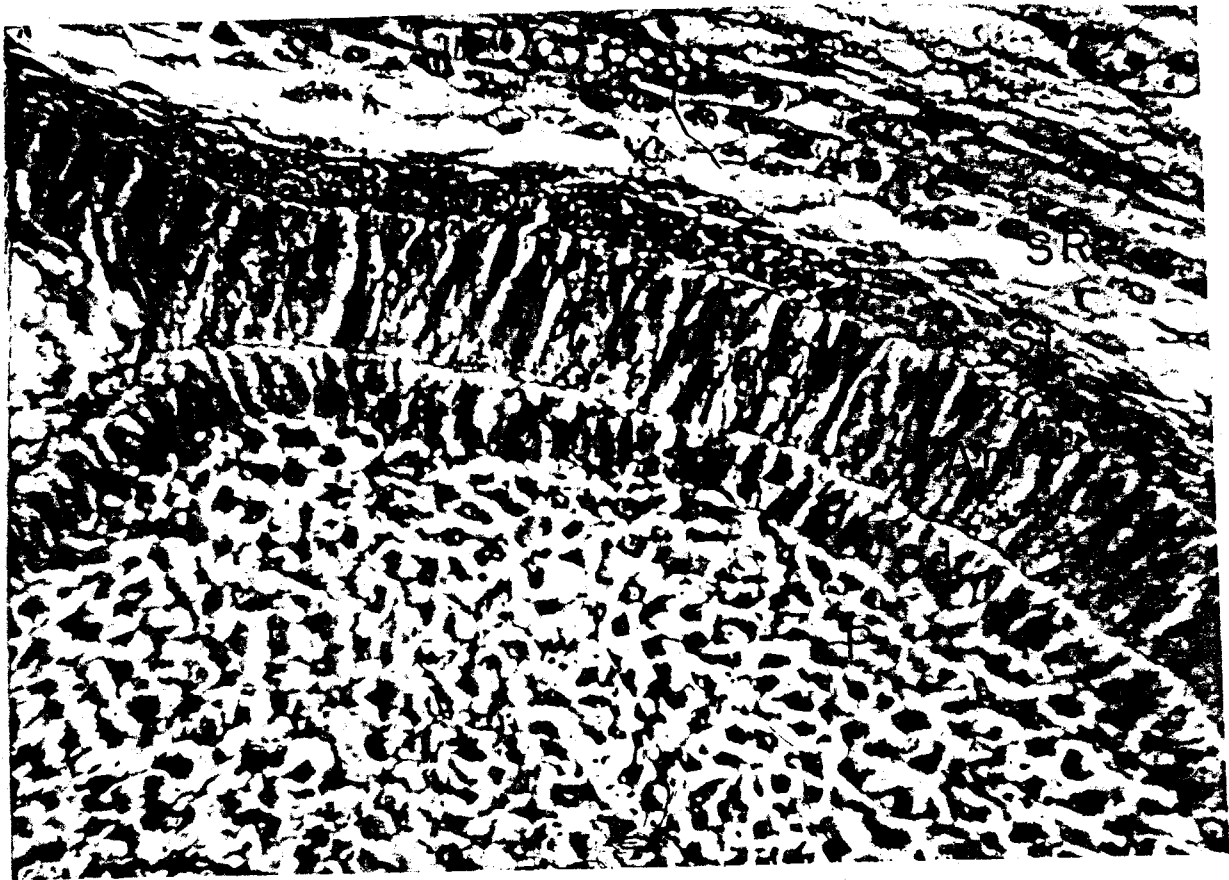


FIGURE 23

PLATE VII

Figure 24. Odontoblastic and ameloblastic epithelium from a maxillary incisor of a rat, 19 weeks following hypophysectomy at 26 days of age. (x360)

Abbreviations: Am - Ameloblasts (proliferating)
Od - Odontoblasts (proliferating)
P - Pulp
SI - Stratum Intermedium
SR - Stellate Reticulum

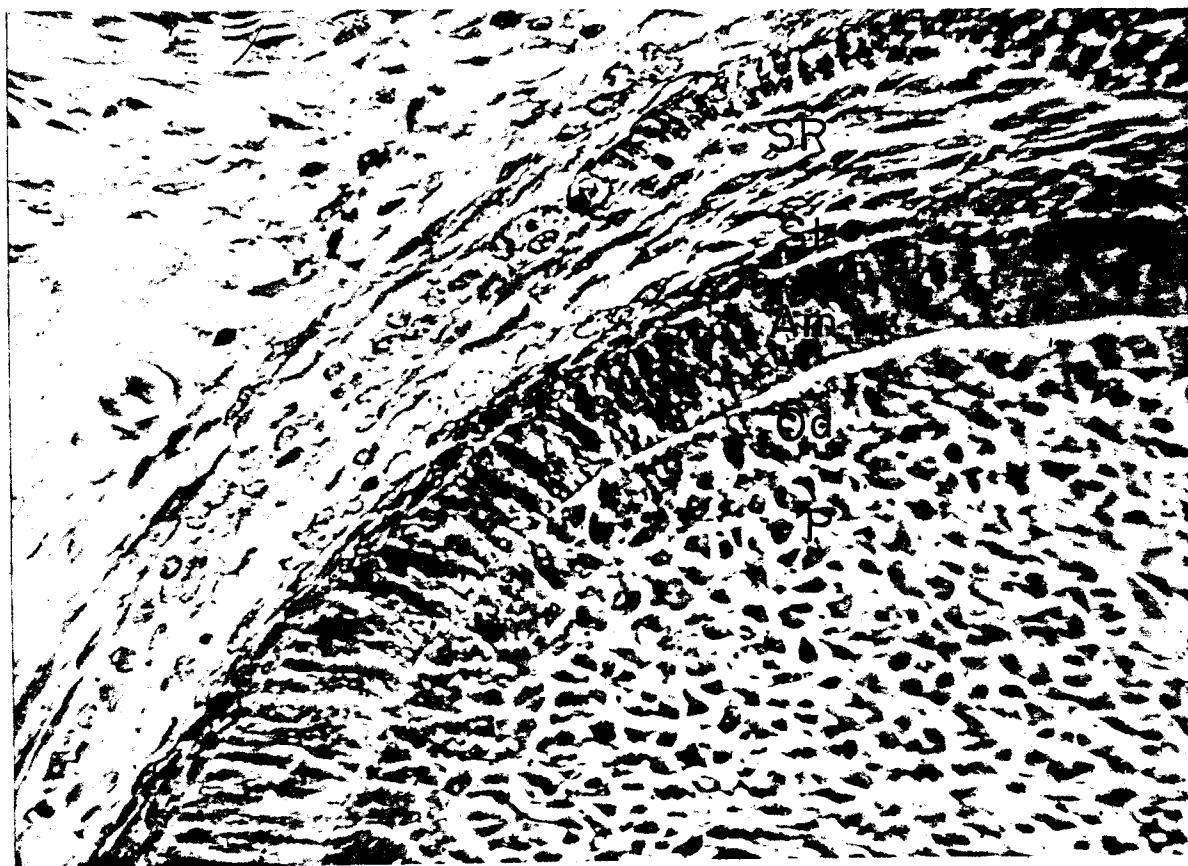


FIGURE 24

PLATE VIII

Figure 25. Odontoblastic and ameloblastic epithelium from a maxillary incisor of a rat, 19 weeks following hypophysectomy at 26 days of age and daily administration of 1.5 mg cortisone for the final seven weeks. (x360)

Abbreviations: Am - Ameloblasts (proliferating)
Od - Odontoblasts (proliferating)
P - Pulp
SI - Stratum Intermedium
SR - Stellate Reticulum

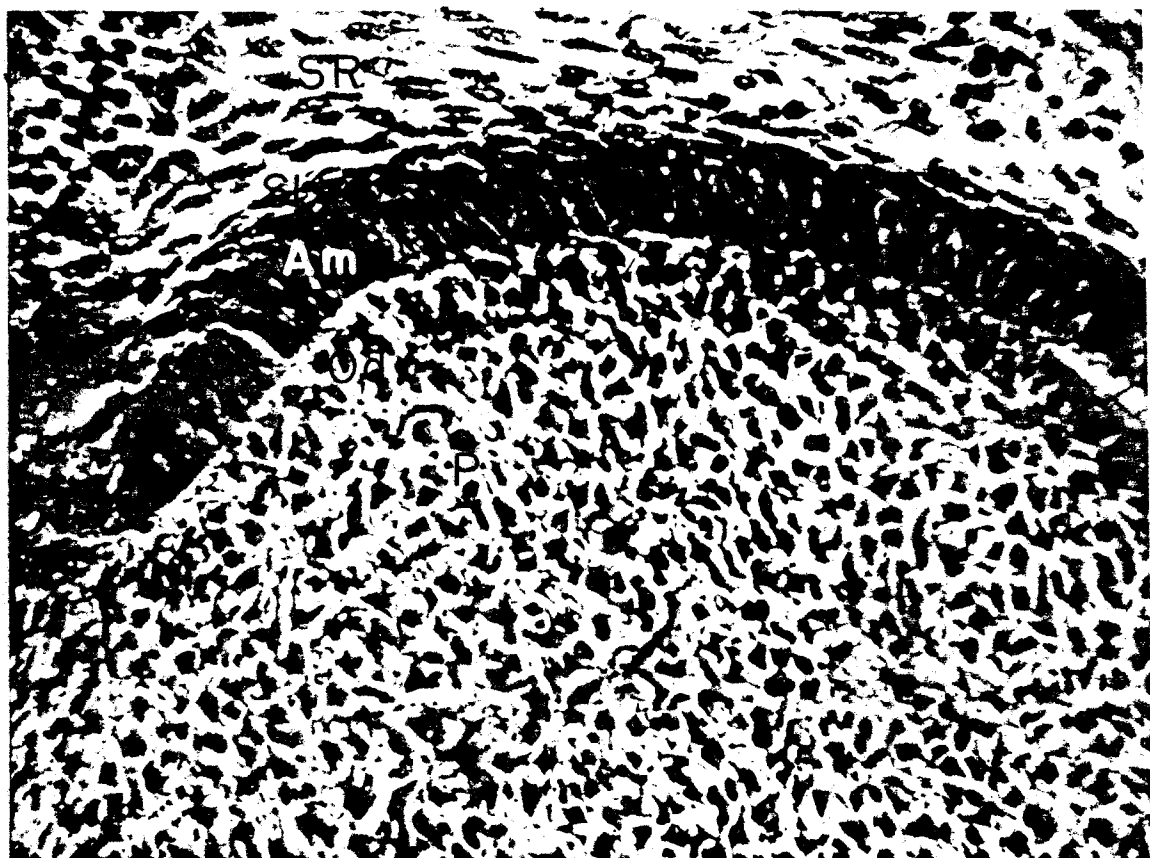


FIGURE 25

PLATE IX

Figure 26. Odontoblastic and ameloblastic epithelium from a maxillary incisor of a rat, 10 weeks following hypophysectomy at 40 days of age and daily administration of cortisone at doses of 0.5 mg for six weeks followed with 0.25 mg for the final four weeks. (x360)

Abbreviations: Am - Ameloblasts (proliferating)
Od - Odontoblasts (proliferating)
P - Pulp
SI - Stratum Intermedium
SR - Stellate Reticulum

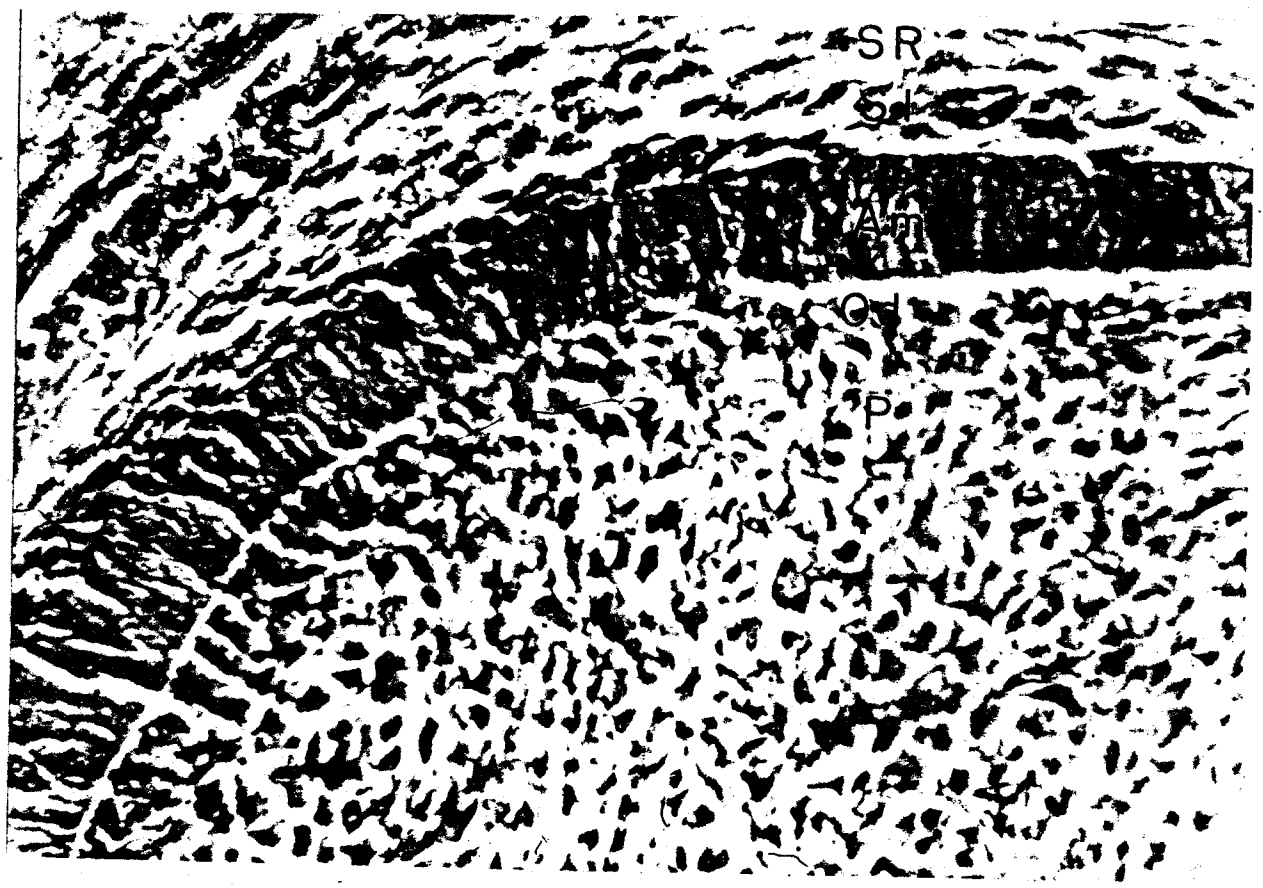


FIGURE 26

PLATE IX

Figure 26. Odontoblastic and ameloblastic epithelium from a maxillary incisor of a rat, 10 weeks following hypophysectomy at 40 days of age and daily administration of cortisone at doses of 0.5 mg for six weeks followed with 0.25 mg for the final four weeks. (x360)

Abbreviations: Am - Ameloblasts (proliferating)
Od - Odontoblasts (proliferating)
P - Pulp
SI - Stratum Intermedium
SR - Stellate Reticulum

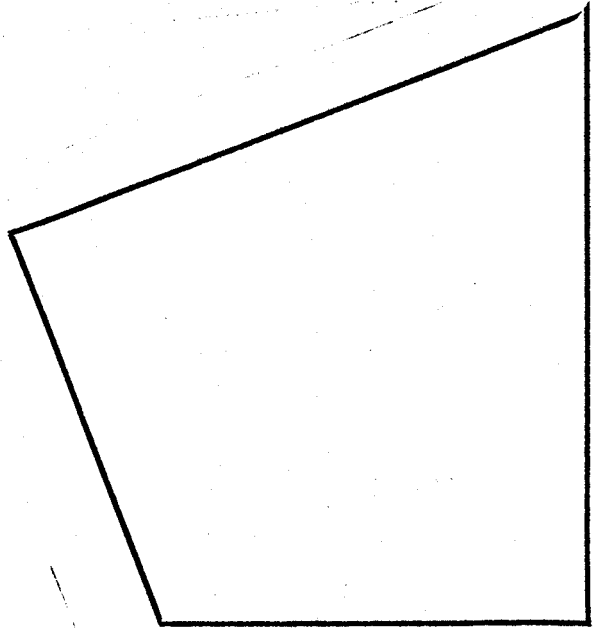
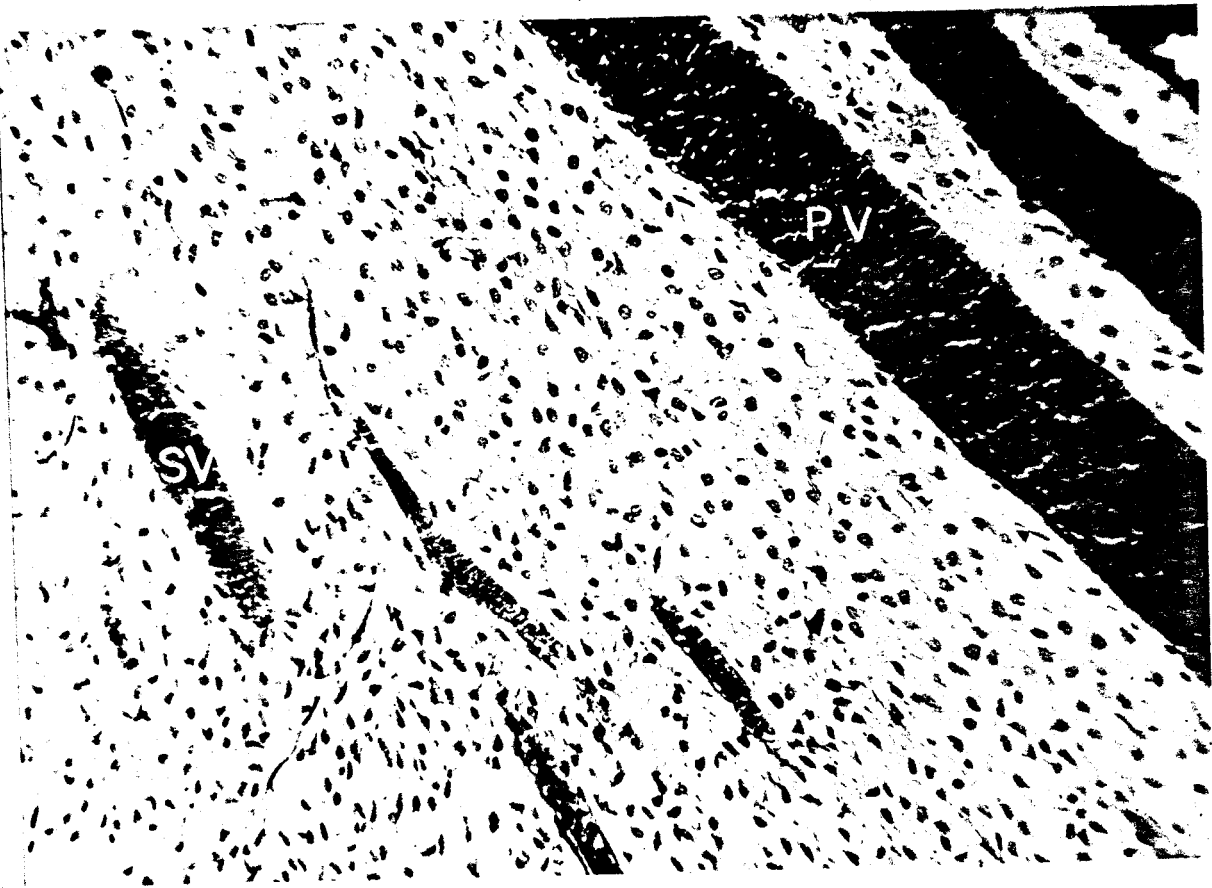


PLATE XI

Figure 28. Pulpal blood vessels from a maxillary incisor of a rat, 19 weeks following hypophysectomy and the daily administration of 1.5 mg cortisone for the last seven weeks. (x150)

Abbreviations: P - Pulp
PV - Primary Vessel
SV - Secondary Vessel



FIGURE 28

PLATE XII

Figure 29. Amorphous clot material in the distal end of the central
pulpal blood vessels from a maxillary incisor of a normal
rat. (x360)

Abbreviations: CM - Clot Material
P - Pulp



FIGURE 29

PLATE XIII

Figure 30. Clot material in the distal end of pulpal blood vessels in a maxillary incisor of a cortisone-treated intact rat. Note the increased density of the material in the lower right side of the photograph. (x150)

Abbreviations: CM - Clot Material
P - Pulp

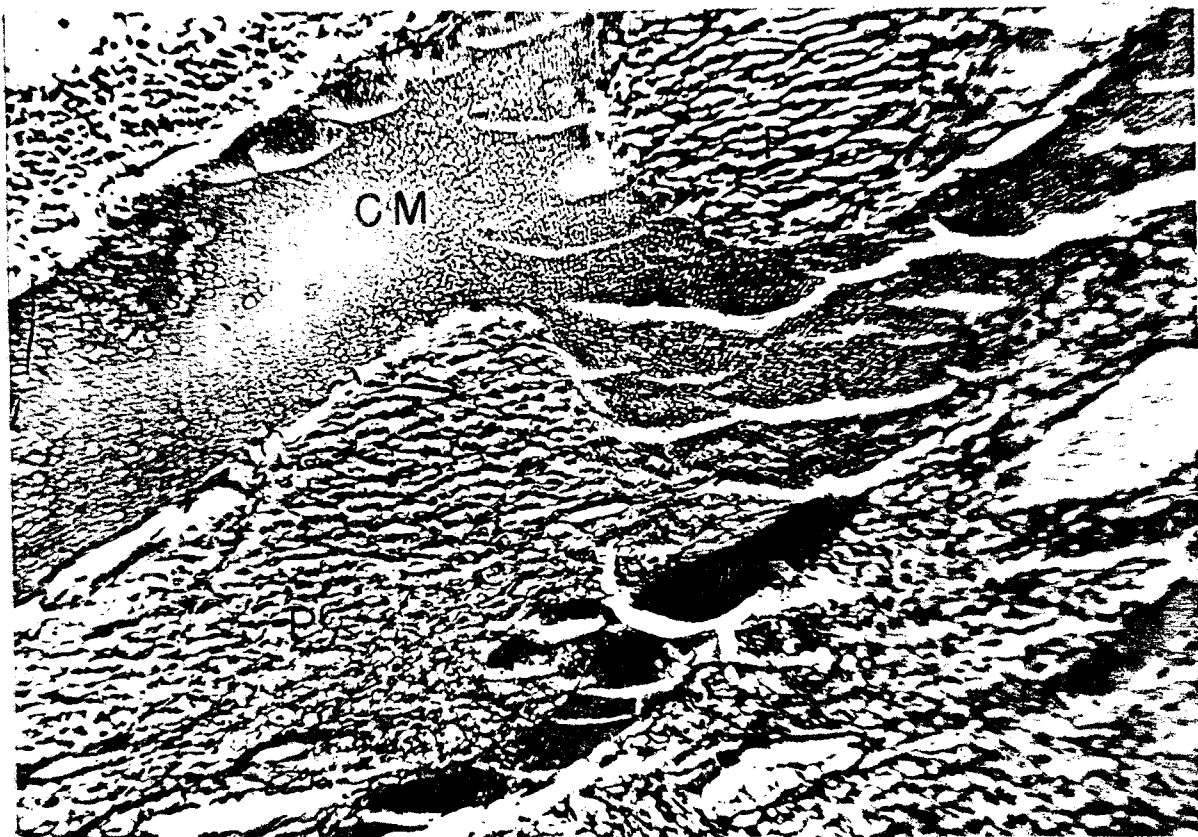


FIGURE 30

PLATE XIV

Figure 31. Clot material in the distal end of pulpal blood vessels in a maxillary incisor of a rat, following hypophysectomy and cortisone treatment. Note the density of the material. (x150)

Abbreviations: BV - Blood Vessel
CM - Clot Material
P - Pulp



FIGURE 31

PLATE XV

Figure 32. Abnormality in dentine formation in a maxillary incisor of a rat, following thyroidectomy at 90 days of age and adrenalectomy, eight weeks later. Note the irregular strip of dentine extending into the pulp. (x150)

Abbreviations: A - Artifact due to shrinkage
Am - Ameloblasts
D - Dentine
Od - Odontoblasts
P - Pulp

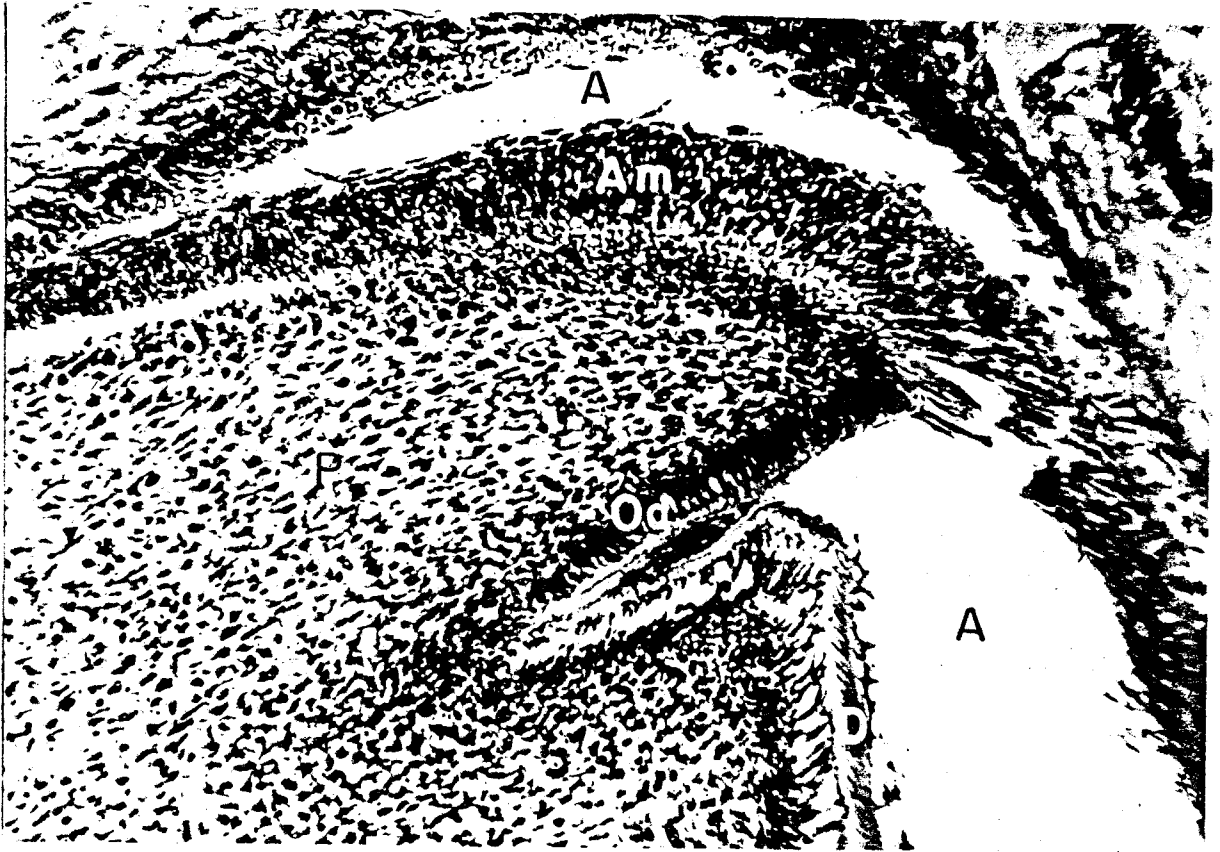


FIGURE 32

PLATE XVI

Figure 33. Abnormality in dentine formation in a maxillary incisor of a rat, following thyroidectomy at 90 days of age and daily administration of 1.5 mg cortisone for six weeks. Note folding of dentine into the pulp. (x150)

Abbreviations: A - Artifact due to shrinkage
D - Dentine
Od - Odontoblasts
P - Pulp

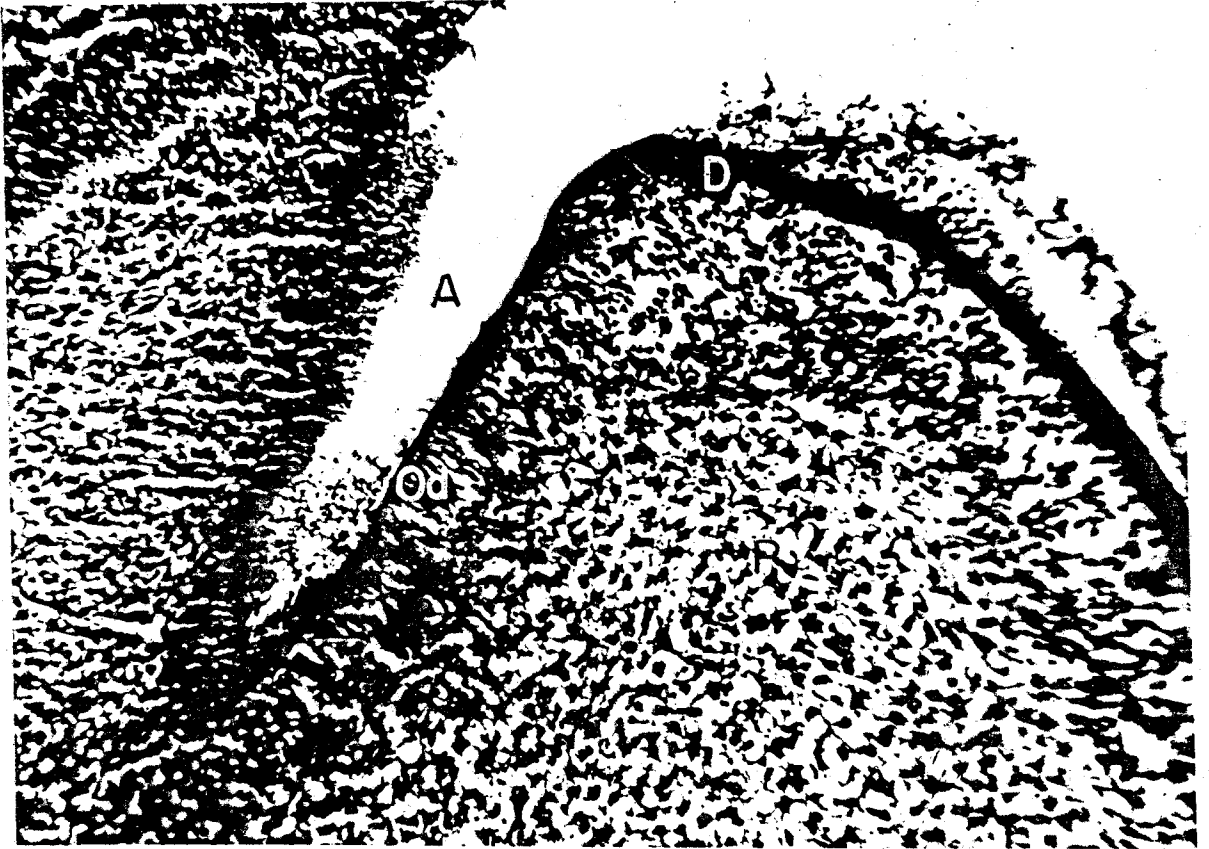


FIGURE 33

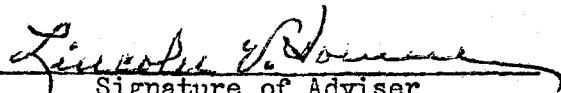
APPROVAL SHEET

The dissertation submitted by Wilbur A. Wellband has been read and approved by six members of the faculty of the Graduate School.

The final copies have been examined by the director of the dissertation and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the dissertation is now given final approval with reference to content, form, and mechanical accuracy.

The dissertation is therefore accepted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

DATE May 30, 1961


Signature of Adviser