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The Hypophysis and the Teeth*

III. Changes in the Rat Molar Following Hypophysectomy

ISAAC SCHOUR, B.S., D.D.S., M.S., Ph.D.
Department of Dental Histology, University of Illinois, College of Dentistry
Chicago, Illinois

The experimental findings in the molars of the hypophysectomized rat are of special interest to the investigator and the clinician because these teeth are similar to the human teeth in respect to their limited growth and the distribution and structure of their tissues. Therefore, the changes in the molar of the rat give us, in some respects, more valuable clues on the influence of the hypophysis on the human teeth than do those in the incisor of the rat.

When first studied it appeared that the molars, which have usually attained most of their growth before the operation, were unaffected by hypophysectomy. However, a more careful study based on a greater number of animals, revealed a series of changes that were strikingly parallel to those of the rat incisor.

This report is made with the primary purpose of describing, briefly, the changes observed in the dental tissues. The discussion will be confined to a few of the points in question. For a description and discussion of some additional features, the reader is referred to another paper (Schour and van Dyke, 1934). A more detailed and more complete account at the present time would lead to a lengthy discussion of many controversial and little known phases of the histo-pathology of dental tissues. Therefore, it is believed that a complete discussion will be more properly indicated when additional material will be available and further studies will be made by various investigators.

*This is the third of the series published in successive issues of the Angle Orthodontist.

Gross Findings

The findings were obtained chiefly from the upper molars because the picture in the lower molars is often obscured by the incidence of caries and because the mandibles were sectioned primarily for the histologic study of the incisor (Fig. 1). A comparison of the radiographs of the experimental and control animals indicates no apparent differences in the size or shape of the coronal portions. However, a shorter length of the roots and a wider pulp chamber, pulp canal, and apical foramen are apparent in the molars of the hypophysectomized rats.

Figure 1
Photomicrograph of a bucco-lingual section of the lower right mandible of hypophysectomized rat 108. X25. This animal was 36 days old when operated upon and lived 273 days following the operation. Note the destruction of the crown of the molar by caries (above); the prominent reduction of blood supply; the reduction of the size of the pulp of the incisor (below); and the distortion of the apical portion of the buccal root to the left at X.

In order to check these observations and make them more objective and accurate, measurements were made directly from radiographs which were enlarged three times. Measurements were also made from the histologic sections. The mesio-distal width of 16 upper molar groups (ten from the experimental and six from the litter mate control animals) obtained by measuring, on enlarged (X3) radiographs, the linear distance between the most mesial point of the first molar to the most distal point of the third molar is practically the same for the experimental animals and their litter mate controls.

Thirty-three upper molars (fifteen from the experimental and eighteen from litter mate control animals) were removed from the maxillae and freed of their investing tissues. The lengths of the roots of these teeth were then measured under the dissecting microscope by means of a caliper. The root lengths upon comparison with corresponding roots of controls were found to be approximately 10-15% shorter in the experimental animals.

The clinical literature contains reports of smaller size of teeth in hypopituitary conditions. Our findings of a smaller size of the roots, only, but not of the crowns is, therefore, of special interest.

It was not possible to obtain quantitative data on the width of the pulp canal and apical foramina by the use of the radiographs or the extracted teeth. Measurements in the histologic sections, however, indicate that the pulp canals and apical foramina are somewhat wider in the experimental animals.

A study of the radiographs shows that in a number of cases the distance between the root ends of the lower molars and the lingual or concave surface of the lower incisors is greater in the experimental animals than in the control animals.

Caries: Radiographic and gross examination of the lower molars of the experimental animals and litter mate controls shows an absence of caries-like destruction in the animals that are not more than about 200 days old and a high incidence of extensive caries in both control and experimental animals above this age (Fig. 1). The radiographs show no caries in the upper molars at any age except in two experimental animals. We are led to the conclusion that the caries in the experimental animals is not significantly different in amount and quality from that observed in the litter mate controls.

Eruption

Unfortunately we did not measure quantitatively the rate of eruption of the molars, as was the case in the incisors of the rat. However, a study of the upper molars with the dissecting microscope discloses a definite retardation of eruption of the molars in the experimental animals (Figs. 2 and 3). This is the case in spite of the fact that one could expect an "elongation" in view of the lack of antagonists because of the destruction of many lower molars by caries.

It is apparent that the state of eruption of the molars at the time of the operation tends to be the permanent condition. This is the case particularly in the third molar which normally is the last to erupt and which in some cases was just becoming exposed to the oral cavity at the time of the opera-

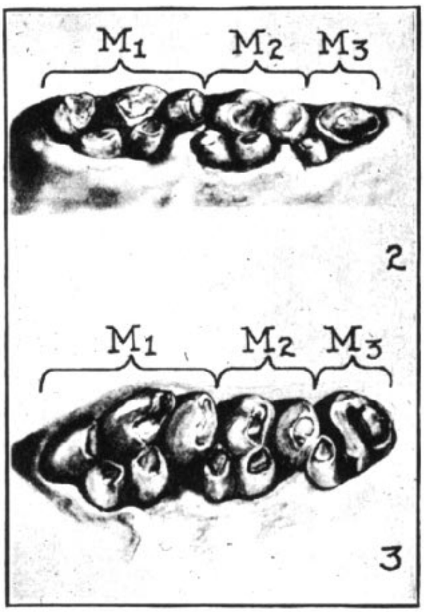

Figure 2

Drawing of the gross occlusal and somewhat lingual view of the upper left first (M. 1.), second (M. 2.) and third (M. 3.) molars of hypophysectomized rat 108. This animal is a litter mate to hypophysectomized rat 113. Note the retarded eruption of the teeth, particularly of the third molar and compare with figure 3 of a normal rat. X 7.5.

Figure 3

Drawing of the gross occlusal and somewhat lingual view of the upper left first (M. 1), second (M. 2) and third (M. 3) molars of a normal rat. Compare the state of eruption of the molars with that shown in figure 2. X 7.5.

tion and, therefore, shows the most prominent retardation of eruption. On the basis of the findings, we feel justified in assuming that if hypophysectomy were attempted successfully in rats at the age of 25 days or earlier, the third molar would not erupt throughout the duration of post-operative life. The histologic findings corroborate the gross findings.

Changes in the Molars of a Representative Rat (Animal 108)

In order to facilitate the description of the histologic as well as the gross findings, the reaction in rat 108 will be given in some detail. This animal was operated upon when 36 days old and its post-operative life was 273 days. Study with the dissecting microscope shows a definite retardation

4

5

Figure 4

Distal portion of upper first molar of control rat 202. Semi-diagrammatic reconstruction of photomicrograph. X 42. Mesio-distal section. Note the constriction of the pulp chamber, p, pulp canal and apical foramen, af; the extensive amount of secondary cementum, *sc;* the good blood supply of the soft tissues; primary cementum, *pc*; secondary dentin which has filled the pulpal horns, *sd;* alveolar bone, *alb*. Compare with figure 5.

Figure 5

Upper third molar, M3, of hypophysectomized rat 108 (same animal as in figures 1 and 2). X 50. Semidiagrammatic reconstruction of photomicrograph. This rat died at the age of 309 days but this histologic picture is that of a much younger animal. The retarded eruption of the third molar is indicated by the common level of the distal gingival margin, *gm,* and the occlusal surface of the tooth. Note in the third molar, the atrophy of the epithelial attachment, *ept;* the height of the pulpal horns, *ph;* the reduced blood supply of the gingivae, periodontal membrane and pulp; the increase in number and size of the epithelial rests, *epr;* the wide pulp chamber, pulp canal, *p,* and apical foramen, *af*; and the scant amount of secondary cementum, *sc*; alveolar bone, *alb*. Compare with figure 4. Figure 6 shows magnified field of bifurcation region.

of the eruption of the upper molars, especially the third (Fig. 2). This observation is confirmed in the histologic sections. Mesio-distal sections show that the crest of the gingivae distal to the third molars is at the level of the occlusal surface of this tooth (Fig. 5). Transverse sections show that the gingival crest buccal to the third molar is also at about the occlusal level.

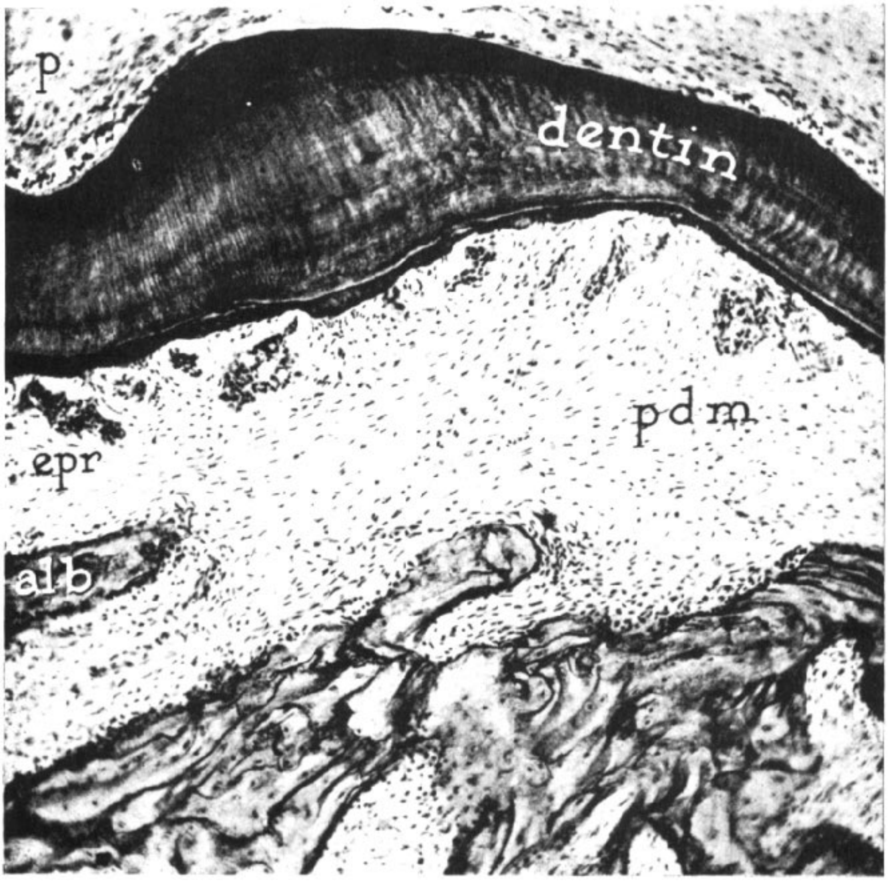

Figure 6
Photomicrograph at a higher magnification of a field from the bifurcation region of figure 5. Note the number and proliferation of the epithelial rests, *epr*, the alveolar bone, *alb*, and the reduced blood supply of the pulp, *p*, and the periodontal membrane, *pdm*. X 280.

A low power field of the third molar of this rat shows a number of features that are characteristic of hypophysectomy. Although the animal was 309 days of age at the time of death, the histologic picture shown in figure 5 resembles one belonging to a rat that is only about 50 days of age or younger. We see a striking persistence of the following juvenile characteristics:

a. Eruption is not yet completed.
b. The pulp chamber and pulp canal are wide.
c. The apical foramen is wide.
d. Secondary dentin at the pulpal horn is absent.
e. Secondary cementum, which normally widens to a prominent knob-like thickening in the apical third of the root, is scant in amount.

In contrast to these juvenile characteristics, we find in figure 5, also, the following pathological features:

a. The absence at the gingival half of the crown of the epithelial attachment and the replacement of the latter by a cementum spur.
b. The severe reduction in the blood supply of the pulp, periodontal membrane and gingival tissue.
c. The abnormal increase in epithelial rests. (Fig. 6.)

Other features found in hypophysectomy are seen more clearly in the material obtained from other experimental animals and will be discussed separately.

Changes in the Enamel

In the molars, the enamel was completely formed and calcified before the operation and therefore showed no disturbance in structure and calcification. However, in eight of our experimental animals, enamel was found to be absent in circumscribed regions near the cemento-enamel junction and replaced by connective tissue. We are dealing here with resorption of enamel that was not exposed to the oral cavity and that lost its normal epithelial attachment. When the enamel comes in direct contact with connective tissue, the latter tends to lay down a cementum spur, as was the case in rat 108, or resorbs the enamel (Gottlieb). This resorption process may continue until it extends beyond the dento-enamel junction. In this event, dentin is also resorbed (Fig. 7).

These resorption phenomena in the crowns of the molars might be confused with enamel hypoplasia or with caries. We are not dealing with enamel hypoplasia because enamel formation and calcification had been completed before the operation was performed and because in some cases the dentin was also involved. The enamel disturbance in question is not caries. The latter proceeds in characteristic stages which are absent in our material and occurs in locations that are exposed to the oral cavity.

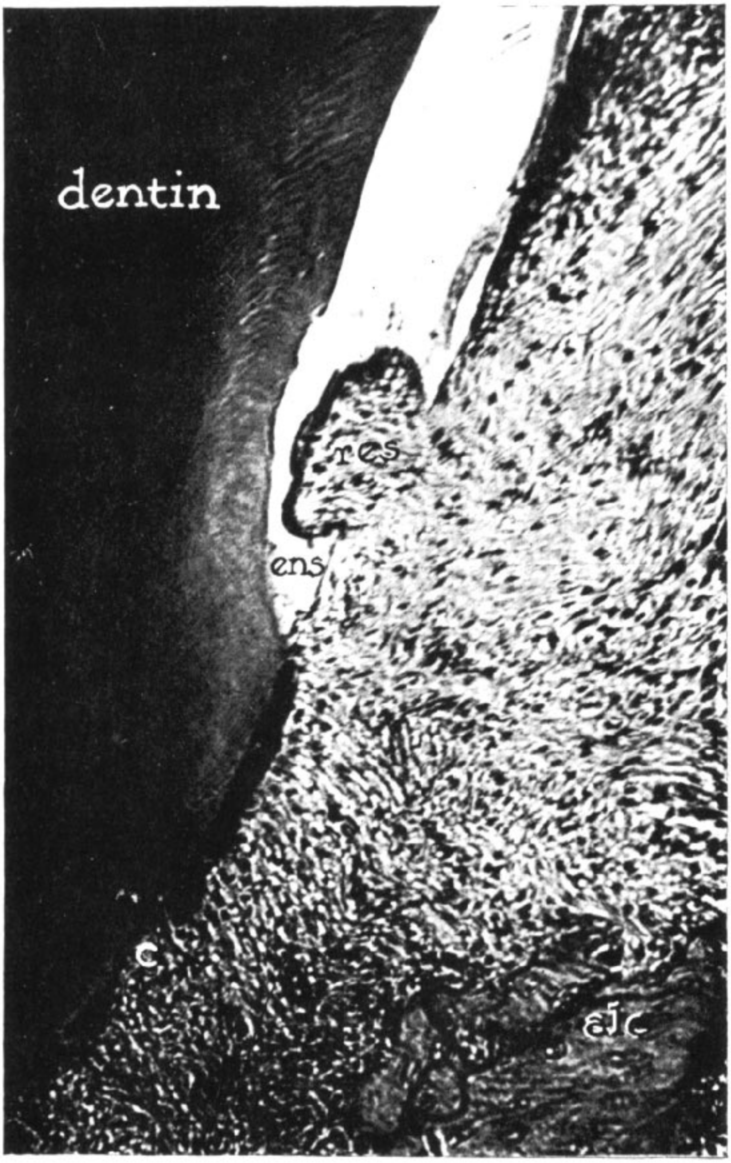

Figure 7
Photomicrograph of a section of the cemento-enamel region of an upper molar of hypophysectomized rat 264 which lived 167 days after the operation. Note the extension of the resorption bay, *res,* to and beyond the dento-enamel junction; alveolar crest, *alc*; resorption of cementum, *c*; and the absence of the epithelial attachment lining the enamel space, *ens*. X 280.

Changes in the Cementum

The alterations in the cementum are of double interest. They indicate disturbances in calcification that are associated with hypophysectomy and, at the same time, help clarify the normal process of formation of cementum and alveolar bone.

The cementum shows resorption at the bifurcation level in the animals of shorter post-operative life. The secondary cementum shows continuous apposition and is free from resorption and yet is considerably narrower than normal. Its retarded growth is chiefly responsible for the finding of shorter roots.

In some of the animals of longest post-operative life, the primary cementum shows, on the surface which faces the periodontal membrane, many globules of various sizes that, like the cementum, take a deep hematoxylin stain and are arranged in the direction of the periodontal fibers (Figs. 8 and 9). Some of these globules are arranged in a bead-like row parallel with the course of the fibers (Fig. 10). In an oblique section of the periodontal membrane and the cementum surface of corresponding sections one can trace the globules as they appear in the center of the fibers, singly or in clusters. Nearer to the cementum surface some of them appear to fuse. Immediately at the surface of the cementum, the entire cross-section of a number of the periodontal fibers appears to have taken on the hematoxylin stain. We are probably dealing here with a pathologic condition of over-calcification. We are also dealing with a pathological disturbance of a phase in the normal mode of formation of cementum which involves the calcification of the periodontal membrane fibers.

Comparison with the Normal Histologic Material

In the effort to evaluate the findings of the globules, which in all probability are calcium globules, in fields similar to that shown in figure 8, it was found necessary to study the cementum surface in the molars of normal rats. This study revealed a process which was fundamentally the same as but less prominent than that first seen in the experimental material.

At or near the cementum surface, the fibers of the periodontal membrane, which take the eosin stain, sometimes in cross section, show small, usually round, hematoxylin-staining globules or granules. These granules are seen to be confined to the cross-sectional area of the periodontal fibers. In some fibers, the granules appear to fuse so that the eosin-staining portion of the fiber is diminished in area and confined to a fine peripheral border. These deep-blue staining areas can sometimes be traced lengthwise in the fibers so that they very likely assume a diminutive form of the fibers in which they are found (Erdheim, 1914).

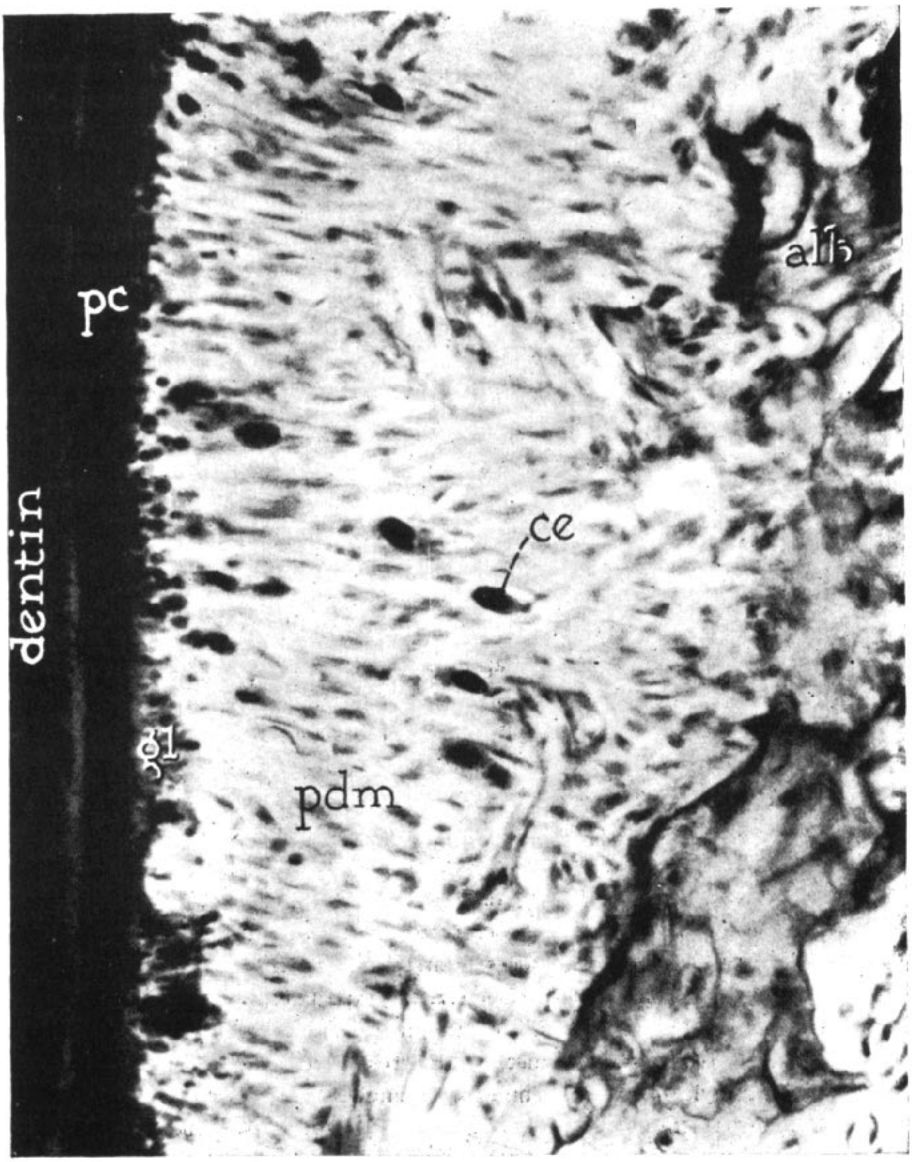

Figure 8
A section of a root of the upper right second molar of hypophysectomized rat 113 which lived 459 days after the operation. X 470. Note the numerous globules, *gl*, at the surface of the primary cementum, *pc*, and the cementicle like structures in the periodontal membrane, *pdm*, toward the right side; *alb*, alveolar bone.

We can only agree with Erdheim who suggests that these areas are possibly calcified portions of the periodontal fibers. A similar phenomenon can often be observed in the cross and oblique sections of the periodontal fibers as they approach and become embedded in the alveolar bone.

Figure 11 is a photomicrograph of a transverse section of alveolar bone obtained from a hypophysectomized animal. This illustration shows the presence of the deep-blue staining globules within the eosin staining body

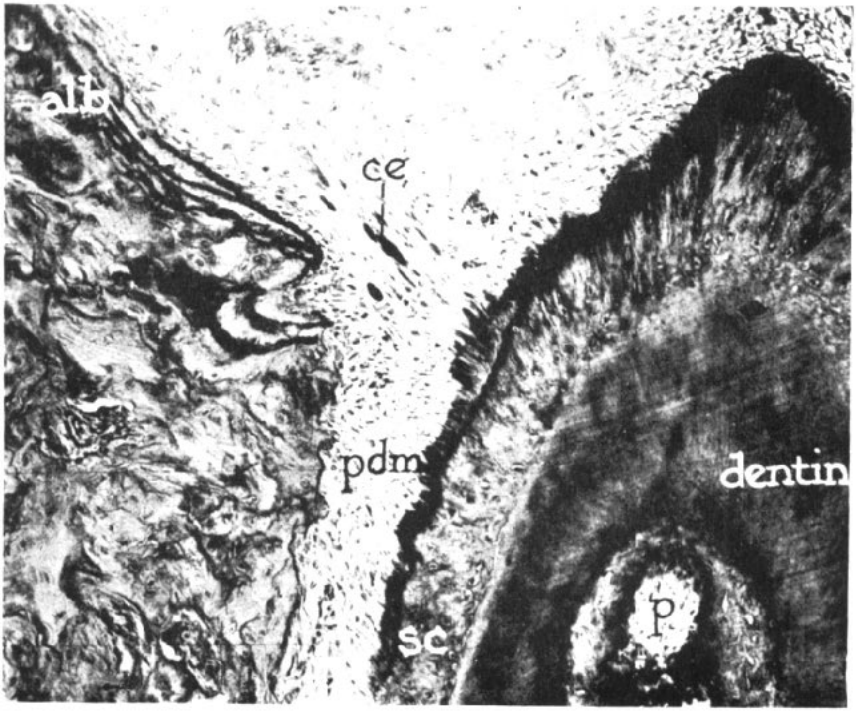

Figure 9
Photomicrograph of an oblique section of a root of a lower molar of hypophysectomized rat 156 which lived 432 days following the operation. X 172. Note the alveolar bone, *alb;* the cementicle-like structures, *ce,* in the periodontal membrane, *pdm,* arranged parallel with the direction of the periodontal fibers; pulp, *p*; and secondary cementum, *sc*.

of the periodontal membrane fibers which are embedded in the alveolar bone. The globules appear to vary in size and number and occupy a greater or lesser portion of the cross section of the fiber. Although this field is taken from an experimental animal, it simply presents an exaggerated picture of the normal process.

Our findings confirm the view of Weidenreich (1926) that the cementum represents the ossification of the inner and the alveolar wall represents the ossification of the outer zone of the periodontal membrane. Thus the formation and calcification of cementum or alveolar bone involve, fundamentally, a process which is similar to that concerned with the formation of fiber bone or with the calcification of tendons, namely, the calcification or ossification of connective tissue fibers (Weidenreich, 1930).

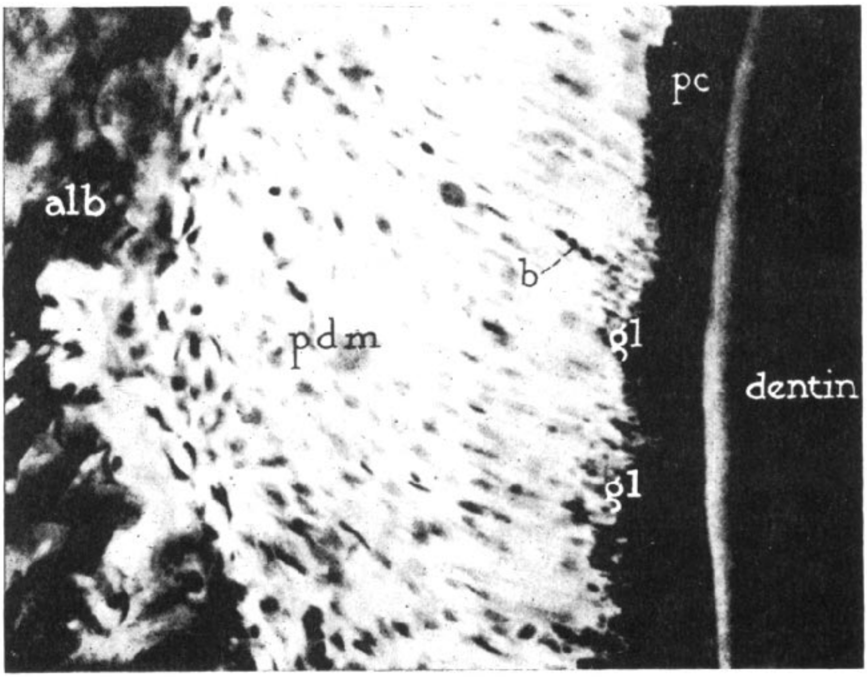

Figure 10

Photomicrograph of section of upper right molar of hypophysectomized rat 113. X 600. Note the alveolar bone, *alb;* the numerous globules, *gl,* at the surface of the primary cementum, *pc*; the bead-like row at *b*; periodontal membrane, *pdm.*

Changes in the Alveolar Bone

In the animals of shorter post-operative life, the alveolar bone shows resorption and activity of giant cells. In the animals of longer post-operative life, the alveolar bone presents, in many fields, an increased number and an irregular crowded arrangement of cementing lines. It gives the appearance of bone that has undergone an unusual amount of apposition and resorption. The bone is sclerotic and reminds one of "mosaic" bone, as described by Schmorl (1932). Bone apposition is found to be continuous throughout the entire post-operative life.

The smaller marrow spaces of the alveolar bone tend to be fibrous and often are reduced in size. In one instance. we find in the periodontal membrane next to the alveolar crest a showering out of calcified bodies that are similar to those seen more often near the cementum.

In view of the fact that skeletal growth stops almost immediately following the removal of the hypophysis, it may be surprising that alveolar bone should continue to be apposed throughout life. However, the apposition of alveolar bone is not at all comparable with an increase in length of the long bones. It is an expression of its high adaptability to function and stress which apparently persists even in the absence of the hypophysis. The teeth of the hypophysectomized rat, except in the most advanced stages, continue to perform their function although the latter is impaired. Therefore, the apposition of alveolar bone, particularly at the crest, denotes merely a rearrangement and an adaptation and response to the stress to which it is subjected during the movement of the tooth in function. The molars of the completely hypophysectomized rat are firm and well embedded. If the alveolar bone did not adjust itself to the tooth function by apposition and resorption, the molars would fall out because of lack of attachment.

In spite of continuous apposition, the alveolar bone in the hypophysectomized animal is smaller than normal. The less than normal amount of alveolar bone is probably a result not only of the general retardation of growth but also of the lessened stimulus following the slowing down of the growth and eruption of the teeth.

Periodontal Membrane

The periodontal membrane shows a prominent reduction in blood supply. The epithelial rests are numerous and prominent (Fig. 6). A number of them degenerate and become cystic and a few are calcified.

In the molars of some of the older animals, cementicle-like structures are found in the periodontal membrane that are larger and fewer than the globules found at the surface of the cementum and that react in similar manner to hematoxylin. They are spherical or oval in shape and are usually arranged in the direction of the periodontal fibers. There are also indications, in the advanced stages, that the periodontal fibers are at least partly calcified in the portion situated near the cementum (Figs. 8 and 10).

Table I—COMPARISON of CHANGES in RAT INCISOR and MOLAR FOLLOWING HYPOPHYSECTOMY

	Incisor	*Molar*
Eruption	retarded and finally stopped	retarded (fig. 2)
Size	smaller (one third less than normal)	roots slightly shorter crown normal size (1)
Form	considerable distortion of form	slight distortion of form confined to the apical portion of the root (1) (figs. 1 and 5)
Persistence of juvenile characters	curvature of tooth greater than normal pigment of exposed enamel lighter than normal	shorter roots (fig. 5) wider pulp-chamber, pulp canal and apical foramina (fig. 5)
Radiographic picture	pathognomonic	
Relationship between the tooth and the rest of the jaw	abnormal	abnormal
Enamel epithelium	regressive, most of it finally disappears	epithelial attachment atrophies and disappears in a number of cases (figs. 5 and 7)
Enamel	folded and hypoplastic sometimes resorbed	normal in structure (1) but sometimes resorbed where epithelial attachment is lacking (fig. 7)
	greater than normal in amount (2)	normal in amount
Dentin	normal as a whole but folded and imperfect at basal zone	normal as a whole

	greater than normal in amount (2) sometimes resorbed	less than normal in amount resorbed when resorption progresses from the enamel or cementum (fig. 7)
Pulp	reduced blood supply less than normal in amount (3) abnormal calcification in anterior zone	reduced blood supply (fig. 5) greater than normal in amount occasionally necrotic
Cementum	normal structure as a whole	surface sometimes sprinkled prominently with globules that stain like cementum (figs. 8 and 10)
	greater than normal in amount (2) sometimes resorbed in basal zone	less than normal in amount (fig. 5) resorption common in earlier stages
Periodontal Membrane	reduced blood supply increase in number and size of epithelial rests	reduced blood supply (figs. 5 and 10) increase in number and size of epithelial rests (fig. 6) calcification of portions of fibers (figs. 9 and 10)
Progress of Changes	severity of disturbances progresses with greater length of post-operative life	severity of disturbances progresses with greater length of post-operative life
Effect of Replacement Therapy	eruption accelerated abatement of severity of histologic changes	almost complete recovery of histologic changes with sufficient dosage and number of injections

(1) Differences between the changes found in the incisors and those in the molars because the latter are of limited growth and incisors are of persistent growth. If operations were performed at a time when the molars were still in their embryonic state of development, these differences would be absent or at least lessened.

(2) Found in incisors because of the accumulation of hard tissues which would have been worn off if the rate of eruption were normal.

(3) This may be explained on the basis of the accumulation of dentin and the concomitant dentification of the pulp.

Disturbances in Calcification

There is an apparent contradiction, on the basis of the histologic study of cementum and alveolar bone, between the indications of undercalcification in the animals of shorter post-operative life and the findings of overcalcification in animals of longer post-operative duration. Therefore, it is of special interest that a similar sequence of events has been found in various types of experimental hyperparathyroidism (Selye 1932, Jaffe 1933, Schour and Ham 1933, Schour, Tweedy and McJunkin 1934) and in hypervitaminosis D (Weinmann 1933, Schour and Ham 1933).

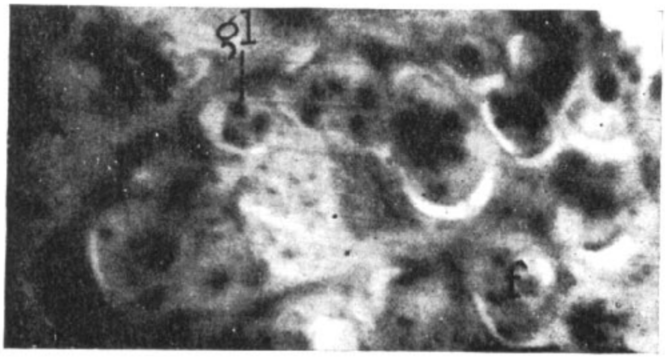

Figure 11

Photomicrograph of a tangential section of the alveolar bone of an upper molar of hypophysectomized rat 221. Note the cross section of the periodontal fibers, *f*, that are embedded in the alveolar bone and that contain hematoxylin staining globules, *gl*, of various sizes. X 1860. These globules may be interpreted as evidence for the calcification of the fibers.

Recent literature has brought increasing indications of the involvement of the parathyroid in the hypophysectomized picture. Atrophied parathyroid glands have been found in hypophysectomized dogs (Houssay and Sammartino, 1933). Cushing (1933) suggests an interrelationship between the hypophysis and the parathyroids. Barker (1933) found a suggestion of tetany in a case of hypophyseal dwarfism. Koster and Geesink (1929) and Evans (1933) refer to a hypocalcemic condition in the absence of the hypophysis, while Gerschmann (1931) reports a normal calcium content in hypophysectomized dogs. Considerable research will be necessary before it will be possible to evaluate the clues found in the dental changes.

Comparison of Changes Following Hypophysectomy in Incisors and Molars

A survey of table I shows that the reaction of the molars and incisors of the hypophysectomized rat are fundamentally the same. Practically all the essential differences may be associated with differences in the physiology of the tooth types. We are dealing on the one hand with the incisor which grows at a rapid rate throughout life. It undergoes some modifications, not only in size but also in shape, so that its alveolar bone is constantly adjusted to these changes. The molar, on the other hand, is a tooth of limited growth. In this investigation, the hypophysis was removed at a time when most of this limited growth had already taken place. Hence, in the molars, the changes were less severe than and in some respects different from those in the incisor and replacement therapy was more successful (Schour 1934).

The findings were:

1. Retarded eruption.
2. Distortion of form in the apical portion of the roots.
3. Persistence of juvenile characteristics; shorter length of roots and wider pulp chamber, pulp canal and apical foramina.
4. Histopathologic changes.
5. Disturbances in calcification.
6. Vascular disturbances.

The data throw interesting light on various phases of the development and eruption processes of teeth.

Summary

The effect of hypophysectomy on the molars of the white rat has been studied in twenty-three completely hypophysectomized rats (63 to 459 days after the operation) and sixteen litter-mate control rats, in respect to rate of eruption and gross and microscopic alterations.

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