Experimental Studies on the Interrelations of Condylar Growth and Alveolar Bone Formation. II. Effects of Growth Hormone

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It is well known that rats of stabilized body weight respond to somatotrophic hormone by resuming growth and may in the course of a year double their weight and size.[1] Growth of bones can be resumed because of appositional growth and because the epiphyseal plates of several bones persist in adult rats.[2] Somatotrophic hormone stimulates growth of the mandible through apposition of bone at the surfaces and borders, and because the growth cartilage of the mandibular condyle persists in rats as in most mammals. The purpose of the present work was to study the interrelations between tooth movements and the growth of the jaws in the adult rat following the induction of growth by somatotrophic hormone.

METHODS AND MATERIALS

The study is based on measurements made on roentgenograms and sections of the alizarin-marked mandibles of twenty-two female rats of the Sprague-Dawley strain, approximately 250 days of age at the beginning of the experiment.

All animals were weighed daily. They were put on a diet of Purina Fox chow and water ad libitum and kept for a ten day period to allow for adjustment to laboratory conditions and to observe their body weight. When this proved to be stationary, all animals were given an injection of alizarin. Five days later, an experimental group of fourteen animals was selected, which consisted of those animals that had shown the smallest weight loss in reaction to the alizarin injection. The remaining eight animals served as controls. The experimental group was given growth hormone for a period of twenty-two days. Twenty-seven days after alizarin and twenty-two days after beginning of growth hormone treatment, control and experimental animals were killed by ether, the heads severed and fixed in 10% formalin. The mandibles were then disarticulated, and roentgenograms of the two halves were made using a standard dental x-ray machine and occlusal film. Next, the mandibles were cut into antemolar, molar-bearing, and postmolar segments. Ground sections of the molar-bearing segments were prepared in the manner reported previously.[3] The sections were ground to a thickness of 250 to 200 microns, dehydrated in alcohols, cleared in xylol and mounted on slides. The postmolar segment of the mandible was similarly cleared for study.

Measurements from Ground Sections

Identical measurements were made for the first and second molar.

Measurements from tracings of projected sections: Tracings of sections enlarged fifty times by means of a micro-

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projector were used to measure dimensions of the crowns and root angles of the molars and bone apposition in the posterior part of the mandible.

Crown height: The occlusal plane of the molar teeth was determined by subjective evaluation of the traced outline of the crowns and a line drawn accordingly. A baseline was drawn parallel to the occlusal plane, passing through the distal cementoenamel junction of the first molar. The height of the crown was measured as the shortest distance between baseline and occlusal surface of the crown as measured along perpendiculars in the center and at the two extremes of the tooth.

Crown length: The length of the crown was determined as the distance between perpendiculars to the occlusal plane drawn as the mesial and distal tangents to the crown.

Root angle: The axis of the distal root was determined by inspection and a line entered into the tracing accordingly. The anterior angle between this line and the occlusal plane was measured.

Bone apposition at posterior border of mandible: Lines corresponding to the deposition of alizarin and to the outline of the bone were traced. To compensate for the medial incurving of the bony margins, tracings were made with the bone tilted to place the alizarin line at the same horizontal level as the edge of the bone. The apposition of bone was measured on the tracing as the distance between the alizarin line and the edge. Growth was measured along four sites perpendicular and four sites parallel to the lower border of the mandible (Fig. 1).

In computing experimental effects, it was assumed that control and experimental animals averaged the same initial dimensions and grew at the same rates up to the time of growth hormone administration, i.e., during the first five post-alizarin days.

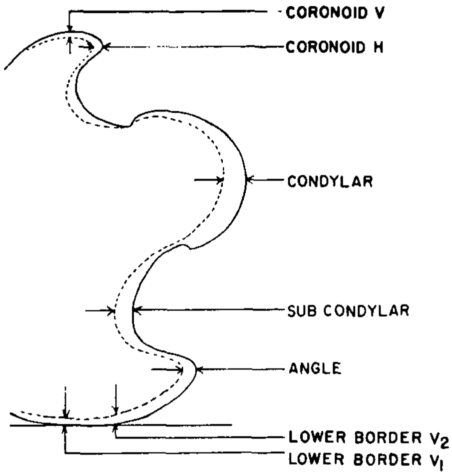


Fig. 1 Diagram illustrating directions and sites used in measuring bone apposition in the postmolar segment of the mandible. - - - - - Alizarin deposition.

Direct microscopic measurements on ground sections: The use of a split image microscope made it possible to take direct measurements of bone growth on the ground sections of the molar-bearing segment of the mandible. A rectangular grid in the ocular of the microscope enables one to set the direction in which measurements are taken. A coordinate system was constructed by using the occlusal plane previously determined on tracings of microprojections of the molar teeth. This was transferred to the image under the microscope by the use of suitable landmarks. Measurements were taken parallel and perpendicular to the occlusal plane.

Growth of bone was measured at the interradicular crest, the fundic area of the distal root, and the posterior border of the interradicular septum.

Growth of cementum was measured perpendicular to the occlusal plane at the apex of the distal root. Cementum apposition in the area of the furcation was not discernible.

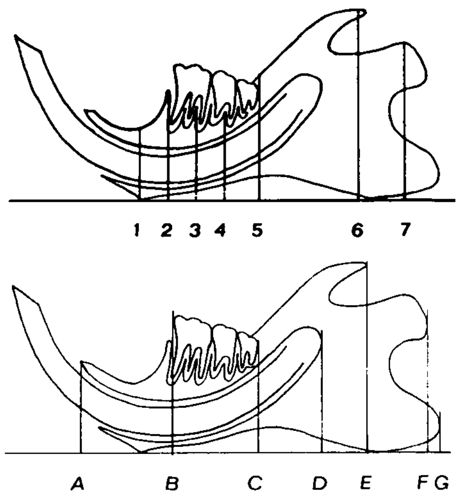
Width of the fundic and interradicular periodontal space was measured perpendicular to the occlusal plane. Details of the methods used in selecting representative sites and in computing tooth movements are the same as in a previous study.[3]

Measurements from Roentgenograms

To increase the accuracy of measurements, enlargements of the roentgenograms (4.5 times) were printed on Kodak commercial ester base film previously found to minimize distortion. A baseline was drawn touching the two lowest points of the lower border of the mandible near the symphysis and near the posterior border. Height measurements were taken perpendicular to the baseline and length measurements parallel to it.

Height measurements (Figure 2): Vertical dimensions were measured at the following landmarks: 1) the anterior lowest point on the inferior border, 2) the highest point of the anterior alveolar crest of the first molar, 3) the highest point of the interradicular septum of the first molar, 4) the highest point of the interradicular septum of the second molar, 5) the projection of the most posterior point of the crown of the third molar, 6) the highest point of the coronoid process, and 7) the highest point of the condyle.

Length measurements (Figure 3): By means of perpendiculars to the base line, the distances between the following points were measured: A. the anterior border of the incisal alveolar bone; B. the anterior surface of the first molar; C. the posterior surface of the third molar; D. the posterior end of the incisor tooth; E. the posterior tip of the coronoid process; F. the posterior surface of the condyle; and G. the posterior end of the angular process of the mandible.



Figs. 2 and 3 Diagrams illustrating sites used in measuring the dimensions of the mandible on roentgenograms. Figure 2 (above): Vertical dimensions. Figure 3 (below): Horizontal dimensions.

Alizarin was given by intraperitoneal injection using a 2% solution of Alizarin Red-S in tap water. The dosage was 1 cc per 100 g of body weight.

Somatotrophic hormone (STH) of the Raben type[4] was obtained through the courtesy of the Wilson Laboratories, Pharmaceutical Division, dissolved to a final pH of 3.5 at a concentration of 10 mg/ml. and given at an initial dose of 10 mg/day per animal, in two subcutaneous injections.[5] The dosage was increased whenever the daily weight gain of the experimental group appeared to level off (Fig. 4). Increases were made three times in twenty-two days, the final dose being about twice that given initially. The object in dosage and mode of administration of STH as well as in the composition of the experimental group was to maximize the action of the hormone.

Findings

Body weight (Figure 4): The experimental group initially averaged 305 grams, the control animals 304. Follow-

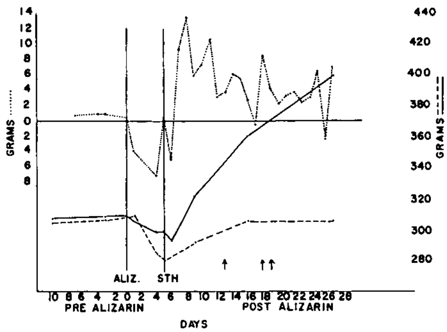


Fig. 4 Graph showing average body weight of experimental (———) and control (- - - -) groups and daily weight change of experimental group (. . . . .). Arrows indicate increases in STH dosage.

ing a ten-day observation period, the experimental animals averaged 309 grams, the controls 308 grams. Both groups lost weight after the administration of alizarin. The lowest weight after alizarin was 293 grams for the experimental group and 280 for the controls. The latter returned to their pre-alizarin weight fifteen days after alizarin, and at the end of the experiment averaged 305 grams. The experimental animals began to gain weight soon after STH administration was begun, reached their pre-alizarin weight after three days on STH, and at the conclusion of the experiment averaged 398 grams. Their average weight increase was 89 ± 5.8 grams, the smallest increase being 38 and the largest 129 grams.

Measurements on Ground Sections in the Molar Area

Changes of crown height and length: A marked experimental decrease in the crown height of the molars was evident. For the first molar, the difference in height of experimental and control crowns averaged 191.6 μ at the distal, 127.8 μ at the middle and 140 μ at the mesial cusp. In control animals, the mesial and distal cusps differed in height by 56.2 μ, while in the experimental animals this difference was 107.7 μ. Thus attrition in the experimental animals was most markedly increased at the distal cusp but was greater at all sites of measurement.

The mesiodistal diameter of the crown was similar in control and experimental animals. The controls averaged 3,003 μ, the experimental animals slightly more, viz., 3,031 μ.

Growth of alveolar bone: Controls: Alveolar bone growth continued at the same sites as in young animals but at a slow rate. Bone apposition occurred along the crests of the bony septa and in the fundic region of the alveolus as well as along the posterior surfaces of the septa, while resorption occurred in the apical half of the anterior surfaces of the septa. The rate of bone apposition at the crest of the interradicular septum was 3,87 ± .24 μ/day, at the fundus 2.25 ± .28 μ/day and at the posterior surface 1.11 ± .13 μ/day.

Experimental animals: STH left the sites of apposition unchanged. The experimental effect was an increase in the rates of bone formation at all sites. The rate at the crest of the interradicular septum was 8.07 ± .49 μ/day, at the fundus 4.15 ± .30 μ/day and at the posterior surface of the septum 1.75 ± .15 μ/day. This represented statistically significant increases in the rates of bone formation of 109%, 84%, and 58% respectively.

Growth of cementum: Apical cementum formation, measured at right angle to the occlusal plane, averaged 2.17 ± .34 μ/day in control animals. The rate in the experimental animals was increased by 64% and averaged 3.56 ± .40 μ/day. The increase was statistically significant.

Width of the periodontal space: Controls: The width of the periodontal space at the bifurcation averaged 108.4 ± 12.9 μ, while that in the apical region was slightly smaller, averaging

103.6 ± 8.4 u. This represents a change of the relation in young animals, where the apical PDS is twice the width of the interradicular. While the interradicular width remains fairly constant between 50 and 250 days of age, the width at the apex narrows to less than half.

Experimental: The width of the PDS in the experimental animals had increased over that in the controls. At the bifurcation it averaged 147.2 ± 14.5 μ. The difference, of 38.8 μ, was of borderline statistical significance. The width in the apical region was 154.0 ± 9.1 μ. This difference, of 50.42 μ, was statistically significant. The more marked experimental change at the apex caused the apical PDS to be slightly wider than the interradicular, whereas the reverse was true in the controls.

Changes in the angle between distal root and occlusal plane: The angle between the mesial aspect of the distal root of the first molar and the occlusal plane was increased in the experimental animals. It averaged 92.13° in the control group and 95.38° in the experimental group.

Changes in position of the molars: Vertical component of tooth movement: If the width of the PDS does not change, vertical apposition of alveolar bone measures the shift in the vertical position of the molars. As reported by Hoffman and Schour[7] and by Schneider and Meyer,[3] apposition at the interradicular crest is by about 15% smaller than the sum of the apposition of apical cementum and fundic bone. The present study showed this discrepancy to be due to the changing width of the apical PDS. Between 60 and 250 days of age, the width of the apical PDS decreases from about 250 to about 100 μ or by about one micron per day. Since the interradicular PDS does not change its width during this age span, interradicular bone apposition is the proper indicator of tooth movement in the vertical direction. In the control animals the vertical movement amounted to 104.5 μ. The sum of cemental and fundic bone apposition was 119.40, i.e., again about 15% greater than the interradicular apposition. The vertical movement was faster in the experimental animals, amounting to 196.9 μ. However, the sum of fundic and cemental apposition, 191.8 μ, was smaller than the interradicular apposition. This finding fits with the more marked experimental widening of the apical than the interradicular PDS.

Anteroposterior component of tooth movement: Although bone apposition at the posterior surfaces of the bony septa was greater in the experimental animals than in the controls, this increase was not associated with a difference in the anteroposterior position of the molars. A widening of the crestal portion of the triangular bony septa is associated with vertical tooth movement. Dependent on the amount of vertical movement, some of the new bone at the posterior surfaces is matched by new bone on anterior surfaces, thus does not change the anteroposterior position of the teeth. This matching amount of bone was computed and found to account for more than the whole experimental increase in bone apposition at the posterior surfaces. STH thus had no effect on the "distal drift" of the molars.

Measurements in the Posterior Area of the Mandible

The control animals showed during the twenty-seven days of observation measurable growth at all sites selected for measurement (Fig. 1, Table I). STH caused variable increases in bone apposition with experimental rates ranging from 125 to 310% of the control rates.

TABLE I

Bone apposition at the postmolar segment of the mandible (Figure 1), total in 27 days, u

	Measurements in vertical direction			
	Coronoid, V	Lower border, V_1	Lower border, V_2	Overall height at condyle
Experimental	143.2 ± 9.49	133.6 ±12.3	300.3 ±20.3	12,587 ±142
Control	113.1 ±15.5	54.2 ± 4.14	110.5 ±26.0	12,588 ±117
Difference	30.1 ±18.1	79.4 ±13.0	189.8 ±33.0	
Difference/day	.42	3.15	7.69	

	Measurements in horizontal direction			
	Coronoid, H	Condyle	Subcondylar	Angular process
Experimental	116.3 ±10.7	495.5 ±21.3	288.3 ±19.1	315.9 ±26.1
Control	76.4 ± 7.59	212.1 ±25.2	114.9 ±21.5	102.0 ±15.5
Difference	39.9 ±13.2	283.4 ±32.9	173.4 ±28.7	213.9 ±30.4
Difference/day	1.2	11.1	6.9	8.9

Vertical measurements: In the vertical direction, apposition was most accelerated at the lower border where the experimental averages were about two and a half times the control averages. A slight increase, by 27%, occurred at the coronoid process also. Because of the inward curvature of the bone at the sites of measurement, the mandible was tilted in order to obtain these measurements. Measurements of the overall height of the mandible taken from an orthogonal projection of the bone showed no difference in height in experimental and control animals.

Horizontal measurements: Measured horizontally, apposition of bone in the controls was slightly less than in the vertical direction. The effects of STH were similarly marked in both directions. At the condyle the experimental animals averaged 495.5 μ, an increase of 234% over the controls. A similarly marked effect was observed at the posterior border between the condylar and angular processes, while the effect was slighter at the coronoid process. The greatest acceleration occurred at the angular process where an increase of 310% over the control average was found.

Measurements on Roentgenograms

Vertical measurements: All vertical dimensions showed an increase in the experimental animals except the overall height at the condyle (Fig. 2, Table II). The maximal increase, by .28 mm, was in the vicinity of the first molar. Slightly smaller increases occurred in the measurements posterior to the first molar. Whereas all other experimental vertical dimensions were by 3-4% larger than in the control animals, the height at the condyle was by 0.6% smaller. This latter finding correlates well with the direct measurements on the mandible.

Horizontal measurements: The experimental animals showed an increase in all horizontal dimensions except the length of the antemolar segment (Fig. 3). The increase was most marked at the angular process, averaging .7 mm, and nearly as marked at the condyle, averaging .6 mm. The difference at the coronoid process was .15 mm. The length of the molar-bearing segment also appeared larger, though the increase was of small magnitude. This agrees with the finding of an increase by 30 μ in the anteroposterior measure-

TABLE II

Dimensions of the mandible measured on roentgenograms at the end of the experiments, mm.

	Measurements in vertical direction (Figure 2)						
	1	2	3	4	5	6	7
Experimental	4.95	7.82	7.35	6.66	7.84	14.42	12.38
Control	4.80	7.54	7.10	6.45	7.60	14.17	12.45
Difference	.15	.28	.25	.21	.24	.25	-.07

	Measurements in horizontal direction (Figure 3)					
	AB	BC	CD	AE	AF	AG
Experimental	7.52	6.76	4.91	21.40	27.48	28.00
Control	7.53	6.73	4.88	21.25	26.90	27.30
Difference	-.01	+.03	+.03	+.15	+.58	+.70

ment of the crowns in the ground sections. The length of the antemolar segment had undergone a very slight decrease. The ratio of lengths of antemolar and postmolar segments was .590 in the controls and .570 in the experimental animals.

Measurements on ground sections in the area of the second molar. All measurements on the first molar were also made for the second molar. The experimental response closely paralleled that on the first molar, as is seen by an examination of Figure 4. The similarity of the experimental effects supported the validity of the observations on the first molar, especially in those instances where differences were too small to be statistically significant.

Discussion

STH and body size

An obvious effect of growth hormone was the gain in body weight of the experimental animals in contrast to the constant weight of the controls. After a day on STH, the experimental group reached its post-alizarin low of 293 grams. Twenty-one days later, the average weight of the group was increased by 36%. Analyses of STH-treated rats have shown decreased fat, but increased protein and water content.[8] While the experimental animals gained 89 grams, the control animals recovered 15 grams of weight lost in reaction to alizarin. Both groups were on a diet of hard food. It is clear that food consumption and masticatory activity of the experimental animals must have been a great deal higher than in the controls.

Role of attrition

Alizarin and x-ray measurements indicated increased vertical and horizontal dimensions of the experimental mandibles with the exception of the length of the antemolar segment and the height at the condyle. Increases were also noted at both molars in fundic and interradicular alveolar bone formation and apical cementum formation; in the width of the apical and coronal periodontal space measured at right angle to the occlusal plane; in the angle between the distal root and the occlusal plane measured anterior to the root; and finally in the apparent length of the crowns measured parallel to the occlusal plane. The height of the molar crowns was found reduced.

One would expect an increased rate of attrition and, therefore, a deficit in crown height in the experimental animals in view of their great increase in food consumption and mastication. The question arises whether the other experimental changes are due to direct effects of STH or secondary to a primary changes, the accelerated attrition.

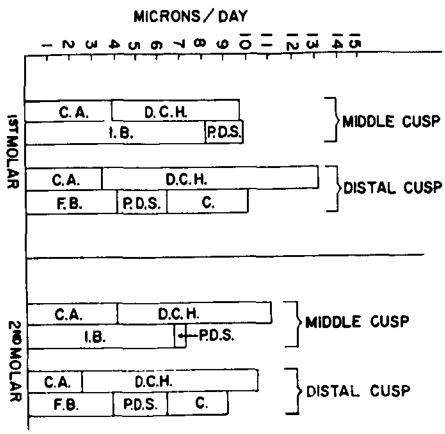


Fig. 5 Diagram showing balance of tooth movement versus attrition at middle and distal cusps of 1st and 2nd molars. For explanation see text.

CA — Control attrition

DCH — Deficit in crown height of experimental tooth

IB — Bone apposition at crest of interradicular septum

PDS — Width of interradicular or apical periodontal space

FB — Apposition of fundic bone

C — Apposition of apical cementum

In order to answer this question with respect to the growth of alveolar bone, a diagrammatic balance sheet of attrition versus tooth movements was constructed (Fig. 5).

Middle Cusp

Attrition: Since only the post-experimental height of the crowns was known, the rate of attrition during the experimental period had to be estimated indirectly. To estimate attrition at the middle cusp, it was assumed that in the controls, in the absence of growth in height of the mandible, the entire vertical component of tooth movement represented compensation for attrition. Control attrition at the middle cusp accordingly was estimated as equal to the amount of interradicular bone apposition, 3.87 μ per day. Experimental attrition at the middle cusp was estimated as being the same as control attrition plus an additional amount, calculated from the experimental deficit in crown height. The difference in crown height of experimental and control animals at the middle cusp was 128 μ at the end of the experiment, an average of 5.81 μ each experimental day.

Tooth movement: Experimental tooth movement at the middle cusp was 8.07 μ of daily interradicular bone apposition plus 1.77 μ of widening of the coronal PDS.

Balance at middle cusp: 9.84 μ of tooth movement against 9.68 μ of attrition.

Distal Cusp

Attrition: In the controls, growth of hard tissues in the fundic region of the distal root served in part to narrow the apical PDS by approximately 1 μ/day. Control growth of cementum plus fundic bone totalled 4.42 μ, of which 3.42 μ are assumed to compensate for attrition. The difference in crown height at the distal cusp averaged 8.71 μ per day. Thus, experimental attrition at the distal cusp was 3.42 plus 8.71 = 12.13 μ per day.

Tooth movement: Experimental tooth movement at the distal root of the tooth consisted of 4.15 μ of apposition of fundic bone, 2.29 μ of widening of the apical PDS, and 3.56 μ of cementum apposition, totalling 10.0 μ per day.

Balance at distal cusp: 10.0 μ of tooth movement against 12.13 μ of attrition.

At the middle cusp the balance of experimental tooth movement against attrition was nearly zero. At the distal cusp tooth movement was somewhat less than attrition. There was, concomitantly, a change in the direction of the occlusal plane of the molars, the distal end being lowered. The mesial angle between the distal root and the occlusal plane was increased for both first and second molars; the antero-posterior length of the molars measured slightly more.

Balance for Second Molar

The numerical relations were not quite as neat for the measurements on the second molar as for those on the first. Since the plane of the sections had been chosen mainly with reference to the first molar, a certain amount of distortion was inevitable in measurements on the second. But both at middle and distal cusps, experimental attrition was increased to an amount not fully compensated by the increase in experimental tooth movement. The imbalance was considerable at the middle and slight at the distal cusp.

STH and growth of alveolar bone

The preceding comparison of the experimental differences in tooth position with the differences in crown height leads to the conclusion that the former can be interpreted as the consequences of the latter. The changes in the position of the experimental molars were such as to compensate almost or entirely for the increase in attrition and the differentially greater attrition of the distal cusp. Since increased attrition commonly leads to accelerated alveolar bone growth, and since the observed acceleration of bone growth did not go beyond the acceleration of attrition, it may not be necessary to postulate a specific effect of STH on the growth of alveolar bone. Whether rats at 250 days of age could have compensated in the absence of STH should be answered by other experiments.

STH and connective tissue growth

There may be more reason to postulate a specific effect of STH on the growth of connective tissue. It was noted that accelerated tooth movement in compensation for attrition involved widening of the periodontal spaces by about 50% in addition to the increased growth of hard tissues. It is true that alveolar bone growth always presupposes the prior proliferation of the connective tissue in the PDL. But this proliferation does not usually lead to widened periodontal spaces since growth of hard tissues keeps pace with it. STH has been shown to have a stimulating effect on the growth of connective tissue.[9] It is not at all clear that, in the absence of the hormone, the periodontal connective tissue would have proliferated to the same extent despite the lag in bone formation.

Age and the potential for bone growth

Even in the presence of STH, the potential for bone growth at 250 days of age might be too small to allow for the required compensatory acceleration. Alveolar bone growth was 209% of control growth at the crest of the interradicular septum and was somewhat less accelerated elsewhere. In a previous experiment animals aged 70 days were found capable of 240% of control growth at the crest of the septum.[3] If the present animals had produced this degree of acceleration of bone growth, widening of the periodontal space would not have occurred. Reduced potential for bone growth might be inferred not only from the widened periodontal spaces, but also from the inadequate bone apposition at posterior surfaces of the septa. There acceleration was sufficient only to take care of the widening of the septa required for the increased vertical component of tooth movement. The increased growth in length at the posterior end of the experimental mandible remained uncompensated by increased posterior drift; this was seen to lead to a slight relative forward shift of the molars.

STH and the role of mastication

In the experiment just referred to,

acceleration of tooth movement occurred in response to reduction in crown height by grinding and persisted until occlusion was re-established. The experiment agrees with the present one in that space for accelerated movement was provided in both. The difference is that in the present experiment space for eruption was provided indirectly through the increased attrition associated with increased mastication, whereas in the previous one space was provided directly and function abolished. It was then concluded that mastication plays a dual role in tooth movement, an inhibitory as well as a stimulating one. The previous experiment revealed the inhibitory role by showing the increased alveolar bone growth in the absence of function. The present experiment showed the inhibiting effect to be smaller than the stimulating effect of masticatory activity when it is associated with increased attrition. The resultant acceleration of bone growth does not correspond to the maximal inherent growth potential. This, rather than advanced age, may be the cause of the lesser acceleration in the present experiment.

STH and the growth of cementum

Cementum responded by greater acceleration of growth to increased attrition than to relieved occlusal stress. Many examples, including orthodontic tooth movement, show that cementum is less responsive than bone to experimentally-induced pressure changes in the PDL. Relief of occlusion may be a case in point. Increased mastication plus increased attrition, on the other hand, might not have changed the balance of stresses, thus resulting in similar effects on both tissues. A stimulating effect of STH on cementum has been noted.[10] It remains an unanswered question whether cementum would have as vigorously responded in the absence of STH.

STH and the dimensions of the mandible

Becks et al.[10] report increased size of the mandible among the prominent increases in intact animals receiving STH, though with distortions in the histology of the condyle. Increase in vertical dimensions in the molar-bearing segment, but no growth in height at the condyle, was observed in the present study. The reason for the latter may be the shorter period of STH administration—twenty-two days as against fourteen months. Alizarin measurements showed increased bone apposition in the postmolar segment of the mandible at the superior as well as the inferior and the posterior borders. The peculiar inward curvature of the new bone prevented a measurable increase in height of the mandible on roentgenograms, whereas the increase in length was clearly discernible. This resulted in a slight change in the proportions of the experimental mandibles.

Increased vertical dimensions in the molar-bearing segment would be expected in the presence of increased vertical movement of the molars. Increased bone apposition at the posterior border would likewise be expected in the presence of increased masticatory activity, muscular hypertrophy and growth of muscle attachment areas of bone. Again the question must remain open whether the magnitude of the observed changes would have been the same in the absence of STH, that is, whether the direct stimulation of appositional growth played a role.

Conclusion

One unquestionable effect of STH was the rapid resumption of body growth which entailed increased masticatory activity and increased attrition. The findings showed near perfect adjustment of the masticatory apparatus to the increased functional demands. There were no major changes in the experimental animals over and above those contributing to the coordinated growth of the masticatory apparatus. It remained undecided whether, given the same primary change due to a different cause, the animals' own regulatory capacities might not have produced the same response in the absence of STH. This conclusion is very similar to the conclusion reached by Evans, et al.[11] in their painstaking comparison of gigantism in hypophysectomized versus intact rats induced by fourteen months of STH administration: "In the growth of the hypophysectomized rats injected with growth hormone many skeletal disproportions developed . . . In the injected intact rats, however, proportionality was maintained in the skeletal growth, almost without exception".

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