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THE EFFECTS OF AVITAMINOSIS AND HYPERVITAMINOSIS A UPON THE INCISOR TEETH AND INCISAL ALVEOLAR BONE OF RATS

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The concept that vitamin A acts on bone formation has been advanced by Mellanby in many publications (e.g. 1938, 1944, 1947), and Wolbach & Bessey (1941) and Wolbach (1946) have also produced theories of a similar nature. Mellanby has reported on the effects of vitamin deficiency and the administration of the vitamin after a period of deficiency. Wolbach and his colleagues have studied both avitaminosis and hypervitaminosis. According to Mellanby (1947), vitamin A governs the action of the osteoblasts and osteoclasts so that bone modelling takes place in an orderly manner. In deficiency of the vitamin, apposition of bone is excessive or may occur on bony faces where usually resorption is found. The osteoblasts and osteoclasts may be reversed in position at the effective surfaces and an orderly disorder occurs. The addition of vitamin A to the diet speedily brings about a return of activity of these cells to the surfaces where it is usually found.

Wolbach (1946) reported that in vitamin A deficiency endochondral bone formation stopped. Appositional bone formation continued until inanition supervened, in strict conformity to the normal growth patterns, both as to situation and to rate, but remodelling sequences, involving concurrent resorption of bone with bone deposition and replacement of cancellous bone by compact bone, ceased.

The toxicity of vitamin A in excessive doses has been investigated by a number of workers, and the literature up to 1945 has been extensively reviewed by Moore & Wang (1945). All writers are agreed that the chief toxic effects are spontaneous fractures of the bones and a tendency to internal haemorrhage. However, many investigators did not consider these actions were due to the vitamin, but to some accompanying impurity. Moore & Wang (1943) were the first to show, by using vitamin A in pure form as a crystalline ester, that the effects of overdosage could indeed be ascribed solely to the vitamin. In further work they confirmed and extended their observations

(1945). Wolbach (1946) reported on the histological changes found in the long bones during hypervitaminosis in rats and guinea-pigs. He concluded that the processes of bone remodelling during growth (epiphyseal cartilage sequences, resorption, and apposition) were greatly accelerated and that the new tissue, hurriedly laid down, was defectively calcified bone or sometimes only osteoid tissue and it fractured easily. van Metre (1947) also found that remodelling processes in the tibia were accelerated in hypervitaminosis A but that longitudinal growth was retarded.

The present paper reports the effects of avitaminosis and hypervitaminosis A on the alveolar bone and upper incisor teeth of rats. Schour, Hoffman & Smith (1941) stated that the socket bone of the incisor teeth appeared thicker than normal with prominent spicules of bone in vitamin A deficiency, and that the growth of the alveolar bone of the molars was retarded. The changes in the incisor teeth in avitaminosis A have been described by Wolbach & Howe (1933), Pohto (1938), Irving & Richards (1939) and Schour *et al.* (1941). The chief action is on the odontoblasts which lay down a defective dentin, and excessively so on the labial side. Later, the enamel organ atrophies and the teeth lose their orange pigment. The effect of excess of the vitamin upon the alveolar bone has not been reported before. Pohto (1938) found that hypervitaminosis A had no effect upon the incisor teeth. Wolbach (1946) stated that the 'sequences of enamel and dentin formation are unaffected, perhaps they are somewhat accelerated'.

METHODS

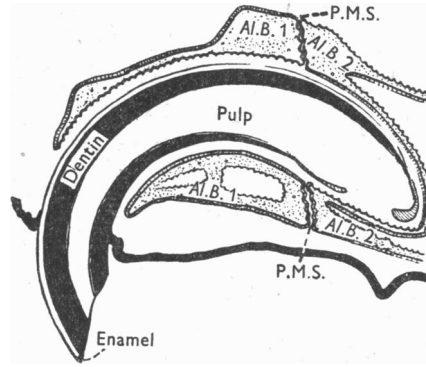
Hypervitaminosis A. Through the kindness of Dr T. Moore, and his associates, the skulls of fourteen hypervitaminotic rats were put at the disposal of the present writer. The experimental details, diet and treatment of the animals were essentially the same as described by Moore & Wang (1945). In brief young rats were given a basal diet similar to that used by these writers, with the inclusion of halibut liver oil in a proportion calculated to provide about 40,000 i.u. of vitamin A daily for from 10 to 42 days. Five control animals received a diet containing arachis oil, in place of halibut liver oil, but a supplement of halibut liver oil was given to each rat so as to supply about 150 i.u. of vitamin A daily.

The heads of the rats were skinned and the skulls were sent from Cambridge to Cape Town in 5% formol-saline. The lower jaws were removed, and the upper portions of the skulls were decalcified and embedded in paraffin. The incisor teeth were cut semi-serially in longitudinal section and stained with haematoxylin and eosin, and also by the method of silver impregnation (Gömöri, 1937).

Avitaminosis A. The tooth sections were from avitaminous rats previously investigated for a different purpose (Irving & Richards, 1939, 1940), and included the periodontal tissues. The diet employed and general management of the animals were the same as described by Irving & Richards (1938). Two different groups of specimens were examined. The first group was of animals on the vitamin A-free diet from weaning for periods of from 28 to 53 days. The second group was of animals on graded doses of the vitamin of from $\frac{1}{3}$ to 4 i.u. daily for from 45 to 180 days from weaning. One rat had been on the vitamin A-free diet from 180 to 450 days of age. Each group had one or more control animals on the basal diet plus 80 i.u. of vitamin A daily. In all, 109 sections were examined.

RESULTS

Growth sequences in the alveolar bone of normal young rats. In order to understand the changes to be reported, a brief description must be given of the normal growth processes. These have been analysed in some detail by Sicher & Weinmann (1944) and by Weinmann & Schour (1945*b*). The alveolar bone consists of an anterior and posterior portion, divided by the premaxillo-maxillary suture, the anterior portion being thus part of the premaxillary bone, and the posterior portion of the maxilla (Text-fig. 1). The alveolar bone is different on the labial and lingual surfaces of the socket. The labial alveolar bone is divided into two almost equal parts by the premaxillo-maxillary suture, whilst this suture cuts through the lingual alveolar wall near the fundus. The fundic plate, a thin layer of bone opposite the basal end of the tooth, is part of the maxilla. On all these various parts of the alveolar bone, an internal, periodontal or alveolar surface, facing the tooth, has to be differentiated from the external surface, which faces marrow spaces, nasal cavity, nasolacrimal duct or forms the outer surface of the bone.



Text-fig. 1. Semi-diagrammatic drawing of the upper incisor of a normal rat. The alveolar bone consists of anterior (premaxillary, *Al. B.*1) and posterior (maxillary, *Al. B.*2) portions, which are separated by the premaxillo-maxillary suture (*P.M.S.*). Scalloped borders indicate sites of resorption; double bars with crossbars indicate sites of apposition. Reproduced with permission from Weinmann & Schour (1945*b*).

Owing to the normal growth and eruption of the tooth, a process of apposition and resorption is continually occurring in different parts of the alveolar bone. Resorption occurs in the premaxillary part of the periodontal face of the labial alveolar bone owing to growth in width of the incisor, while apposition takes place on the external side. Apposition occurs in the anterior part of the periodontal portion of the lingual alveolar bone and in the palatal plate, while resorption occurs in the marrow cavities inside the bone and on the bone surrounding the naso-lacrimal duct, which runs through the bone under the incisor tooth (Irving, Weinmann & Schour, 1947). Owing to its shift towards the tooth by sutural growth at the premaxillo-maxillary suture, the fundic bone is resorbed on the periodontal side, while apposition occurs on the external surface. The maxillary alveolar bone at the labial surface undergoes apposition on the periodontal face and resorption on the other side.

Hypervitaminosis A

Gross pathological findings (as reported by Dr Moore). The control animals were normal in all respects. All but two of the experimental animals had fractures of one or more bones and several had scattered haemorrhages. Three

died spontaneously. Both the blood and liver vitamin A values were considerably raised by the excessive dosage.

Alveolar bone. The most striking feature of the alveolar bone of the hypervitaminotic rats was its abnormal narrowness and fragile appearance as compared with that of the controls. The lingual alveolar bone, especially between the naso-lacrimal duct and the periodontal membrane, was extremely thin, and in some cases was missing in parts (Pl. 1, figs. 1 and 2). The labial alveolar crest was narrower than usual and in some cases seemed to have been split up into fragments.

Closer examination of the various parts of the alveolus indicated that while osteoclasis was proceeding, apposition of bone was in many places lacking. The lingual alveolar bone was bounded on the periodontal side by well-marked resting lines which extended from the alveolar crest to the premaxillo-maxillary suture. The spicules of the suture in the palatal plate were also bounded by cementing lines. The periodontal membrane on the lingual side of the tooth appeared normal.

The labial premaxillary alveolar bone showed osteoclastic resorption of normal intensity along its whole periodontal surface from the alveolar crest to the premaxillo-maxillary suture. Relatively much less apposition than usual appeared to be occurring on the external face. In some areas no apposition was occurring, while in others some osteoid-like material was being deposited. Many more cementing lines than usual were present in the whole labial alveolar bone, indicating that apposition had frequently stopped. The periodontal membrane was normal in all but one rat where it was compressed, probably by collapse of the alveolar bone.

The fundic bone was narrower than normal, in most cases stained more intensely with haematoxylin, and contained almost a mosaic of cementing lines (Pl. 1, figs. 3 and 4). Osteoclasts were present on the periodontal surface.

These changes in the alveolar bone seemed to be equally severe in all rats examined, irrespective of the length of time of hypervitaminosis. They were particularly marked in the rat which had died after 10 days, in which parts of the premaxillary labial alveolar bone were missing. In general, it could be concluded that the chief change was an imbalance of apposition and resorption, the first process being in large measure suppressed, so that the bone became unduly thin. This imbalance was most prominent in the premaxillary alveolar bone and in the fundic bone.

Incisor teeth. The changes in the dentin were best seen on the labial side of the tooth, and the following findings refer to investigations of this area. The time of transference of the rats to the basal diet at the commencement of the experiment was marked by a change in the histological appearance of the dentin laid down at that time. With haematoxylin and eosin, a faint hypocalcified layer followed by a hypercalcified zone was seen; with silver

impregnation a very clear line taking the silver stain less well was visible in all specimens (Pl. 1, figs. 5 and 6). The dentin produced during the experimental period was incrementally laid down in stripes staining alternately dark and light, in almost all teeth, both control and experimental, and the number of stripes when counted equalled the days of the experimental period, thus showing that this was in fact experimental dentin. Measurements of the width of this experimental dentin showed that in the control animals the average daily increment of dentin was 1·6 μ., which is the normal figure. In all the experimental animals the amount of dentin laid down during the experimental period was less than this, and the daily increment was on an average 1·3 μ. In several of the experimental animals the daily increments became narrower as one approached the pulpal side, indicating that the incremental growth of the dentin had gradually slowed down.

The predentin of the teeth of the experimental animals was narrower than normal, especially at the formative end of the tooth. The average predentin width at the formative end of the tooth was 1·8 μ. in the control and 0·9 μ. in the experimental animals. The figures obtained were about the same in all animals examined, irrespective of the length of time of hypervitaminosis. The fact that the experimental predentin width was less than the average daily increment is probably due to the gradual slowing of the incremental dentin formation. The narrow predentin was not the result of an imbalance between calcification and incremental growth. Had this been so, the predentin would have been still narrower, or even non-existent in the animals on the experiment for a long time, which was not the case.

The experimental dentin appeared more compact and stained somewhat more deeply with haematoxylin than the pre-experimental dentin, or than that of the controls. With the silver stain, the experimental dentin first laid down stained less deeply than the pre-experimental dentin, but that most recently formed stained more deeply and contained well-marked strands of fibrils running parallel with the pulpal border (Pl. 1, fig. 6). These were identified as the fibrils normally present in dentin, which were present in higher concentration per unit volume in this area, and which normally take the silver stain; the interfibrillar-cementing substance, which is not stained with silver, was relatively reduced in amount, indicating a decrease in mineral content. This change in the structure of the dentin appeared to coincide with the reduction in daily apposition rate.

The odontoblasts on the labial side of the pulp of the experimental animals were normal in appearance, but those on the lingual side at the formative end were reduced in height and at the epithelial sheath consisted of a line of flattened cells. The average height of these cells in the control animals varied from 25 to 64 μ., while in the experimental animals the corresponding figures were 17–46 μ.

The organic enamel was normal in all the experimental animals. Cysts were present in the enamel organ in two experimental animals. These have also been described by Weinmann & Schour (1945*a*) in rachitic animals and are probably not specific to hypervitaminosis A. The cementum was normal in all cases. In general it could be stated that the changes in the teeth in hypervitaminosis A were much less in degree than those in the alveolar bones.

Avitaminosis A

Alveolar bones. The changes to be described were already visible after 28 days on the vitamin A-deficient diet and became gradually greater with time. The protection afforded by various doses of the vitamin became less as the animals grew older, suggesting that the requirements rise with age (Irving & Richards, 1939).

The changes in the alveolar bones were essentially the same in all animals up to 180 days on the deficient diet, differing only in degree. In general, the chief change was an excess of apposition of bone compared with the opposite process of osteoclasis. Apposition occurred in some situations where normally resorption takes place. This was particularly noticeable at the labial alveolar crest and along the premaxillary labial bone. Here a reversal of the normal process was seen. In the early stages of the deficiency, osteoblasts could be sometimes seen 'elbowing out' osteoclasts on the periodontal surface. By 52 days on the deficient diet, only osteoblasts were seen (Pl. 1, fig. 7) and a wide layer of new bone, apparently normally calcified, had been laid down. On the external side of this bone osteoclasts were found, but here the normally occurring osteoblasts were also seen, and apposition and resorption might occur in adjacent areas.

The maxillary labial bone was almost normal in width in the early stages of the deficiency, but became much wider with marked apposition of new spongy bone on its periodontal surface in later stages. Osteoclasts were present on the opposite face in about normal numbers.

The fundic bone, in later stages of the deficiency, showed apposition on its periodontal face, instead of the usual resorption, and active osteoblasts could be seen (Pl. 1, fig. 8; cf. fig. 3). The new bone was not laid down as a regular layer, but as tongue-shaped outgrowths into the periodontal tissues. It was not uncommon in the early stages to find osteoclasts apparently endeavouring to remove this recently formed new bone and lying in close proximity to osteoblasts. Osteoclasts were sometimes seen in small numbers on the opposite face of the bone, but were not at all conspicuous.

Thus the chief change observed was an excess of osteoblastic activity. In sites where this occurred normally it went on unchecked and osteoclasts never appeared. While in areas where this action was abnormal, osteoclasts attempted in the early stages to remove this new bone being laid down. In

spite of this excessive apposition, bone growth as a whole was retarded (Schour *et al.* 1941).

The one rat examined which had been on the diet from 180 to 450 days of age showed changes somewhat different from those in the younger animals. Active apposition and resorption had largely stopped, presumably owing to cessation of bodily growth, since the same was found in the control animal. The alveolar bone throughout was much thicker and almost unrecognizable in places, consisting of cancellous and compact bone. This was true of the premaxillary alveolar bone on both sides and especially of the maxillary labial and fundic bones which, instead of being thin plates, were replaced by thick aggregates of bone.

Incisor teeth. The changes in these teeth in avitaminosis A have already been described by Wolbach & Howe (1933), Pohto (1938), Irving & Richards (1939) and Schour *et al.* (1941). The same changes were seen in the teeth of the present animals. On the whole, the teeth appeared less sensitive to this deficiency than the alveolar bones, since the teeth of animals killed early in the experiment were normal while the bones were already beginning to show the characteristic changes.

DISCUSSION

Wolbach's (1946) thesis, that resorption ceases in avitaminosis, while apposition continues is not supported by the above findings. Osteoclastic activity was changed and overshadowed by the excessive activity of the osteoblasts, but in no cases had it actually ceased. In addition, his statement that apposition occurs 'in strict conformity to normal growth patterns, both as to situation and rate', is not borne out by the present work, either with regard to situation or to rate. Nor was his concept of hypervitaminosis causing an acceleration of bone remodelling supported by the findings in the alveolar bones, since the present writer found that in such a condition the bones were slowly resorbed.

The changes in the alveolar bones were much more like those described by Mellanby, though here too some differences were discernible. The overactivity of the osteoblasts in normal and abnormal situations was just as described by him. He emphasizes the orderliness of the change in position of the osteoblasts and osteoclasts. His experimental animals were on the deficient diet for a considerable time, showed well-marked signs of deficiency, and the change-over of situation of the osteoblasts and osteoclasts was complete. It is difficult to picture, however, that at a certain time during the deficiency, these cells suddenly change places. The present results show that in the early stages this is not an orderly proceeding, but one in which the osteoclasts compete for their normal position with osteoblasts and are finally ousted. Even on the other surface of the bone, they are found between osteoblasts and their efforts are

quite insufficient to counteract the excessive apposition. Thus in the ultimate stages an appearance of orderly disorder appears to exist, but actually it is due to the preponderance of one type of cell over the other. Mellanby (1947) has advanced some attractive hypotheses to account for the apparent transfer of these cells from one part of the bone to another, but at present very little positive evidence exists to explain this phenomenon.

Mellanby has not reported the effects of hypervitaminosis, but he has investigated the effects of vitamin A administration upon vitamin-deficient animals. From the drawings in his paper (1947) it would appear that the osteoclasts respond with much greater vigour to this treatment than do the osteoblasts. In the present results, the osteoclasts were hardly affected by the hypervitaminosis. The chief feature noticed was the cessation of action of the osteoblasts.

Schour *et al.* (1941) have shown that the effect of vitamin A on the incisor tooth is specifically upon histodifferentiation of the odontogenic epithelium. It is thus of interest that the odontoblasts respond in a way very similar to that of the osteoblasts, and suggests that the underlying processes of differentiation of bone and tooth cells may be comparable. In vitamin A deficiency, the odontoblasts lay down an excessive amount of poorly formed dentin on the labial side of the tooth and may also produce osteoid masses in the pulp. In hypervitaminosis, the odontoblastic activity is damped down, and dentin formation becomes slower. The changes found in the present studies were quite different from those of Wolbach (1946), who stated that, if anything, enamel and dentin formation were accelerated. The quantitative deposition of fibrils does not seem to be reduced, and, as apposition slows, they become more concentrated and are thus more conspicuous, and there is a relative reduction in the amount of interfibrillar cementing substance and thus also in the Ca content per unit volume. If this also occurs in bone in hypervitaminosis, it may account for the increased fragility and tendency to fractures.

From the results reported in this paper it seems legitimate to postulate that the action of vitamin A in bone formation is primarily on the osteoblasts, these cells acting in an uncontrolled way in the absence of the vitamin, and being suppressed in hypervitaminosis. The reactions of the osteoclasts are purely secondary to this: in the former condition their action is quite obscured by the excessive bone production with which they are unable to cope; while in the latter, the osteoclasts work unopposed, removing and weakening bone, and finally causing fractures.

In the case of the teeth, the action of the vitamin is on comparable cells to the osteoblasts, namely the odontoblasts. The reactions of these cells are similar to those of the osteoblasts in the two conditions of vitamin A administration. The absence of cells analogous to osteoclasts makes the picture of the dental changes a much simpler one than that in the bones.

SUMMARY

1. The reactions of the alveolar bone and upper incisor teeth in hypervitaminosis and avitaminosis A have been studied in young rats.

2. In hypervitaminosis the rate of formation of bone is greatly reduced and active osteoblasts become much less prominent. Osteoclasts appear to be unaffected, with the result that the bones become abnormally thin and may disappear in places.

In the incisor teeth, only dentin formation is affected. This becomes decreased in appositional rate, the interfibrillar cementing substance is gradually reduced in amount, and the lingual odontoblasts begin to atrophy.

3. In avitaminosis, the alveolar bones show, in general, considerable overproduction of new bone. This occurs in areas where apposition is usually seen, and also in situations where resorption normally occurs. In the early stages of the deficiency osteoclasts endeavour to overcome the latter unnatural apposition.

The teeth show changes already reported by other workers. These are chiefly in the dentin and odontoblasts, and excessive and faulty dentin formation occurs especially on the labial side.

4. The proposition is advanced that, in bone formation, vitamin A acts primarily on the osteoblasts. Excessive vitamin A in the diet depresses the action of these cells, while, when the vitamin is lacking, these cells engage in disorderly overactivity. The reactions of the osteoclasts in avitaminosis are purely secondary in an attempt to prevent excessive bone formation. In hypervitaminosis these cells continue to act as usual. The odontoblasts, cells in the teeth comparable to the osteoblasts, react in a way similar to that of the bone-forming cells, producing less dentin in hypervitaminosis, and excessive amounts in avitaminosis.

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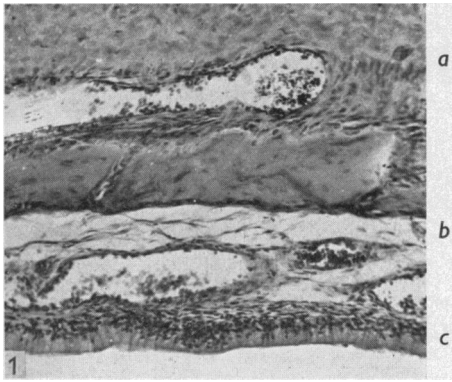

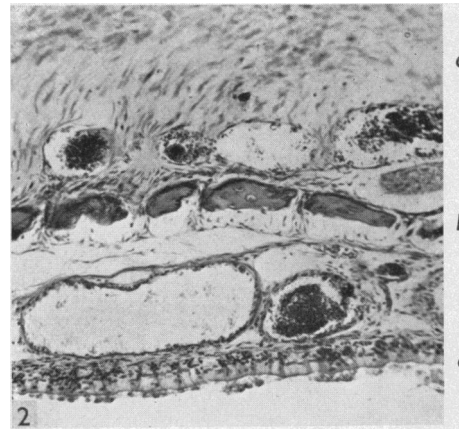

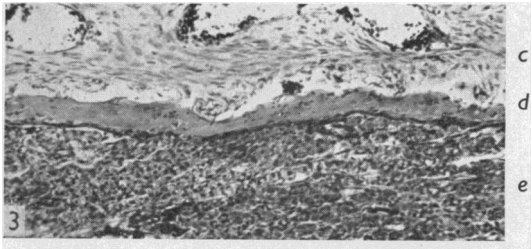

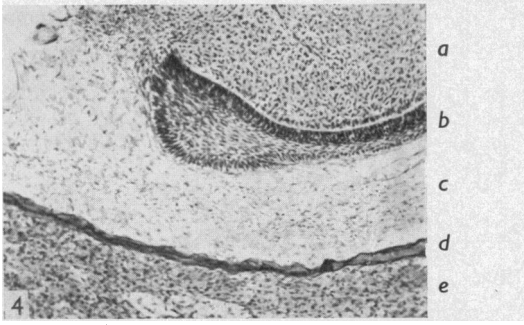

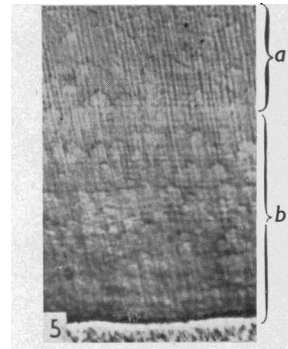

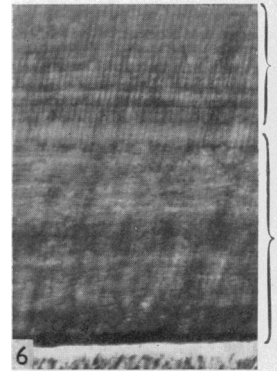

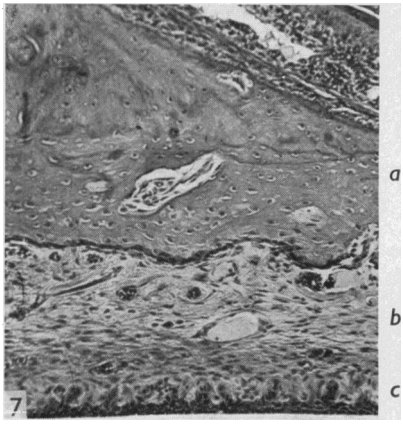

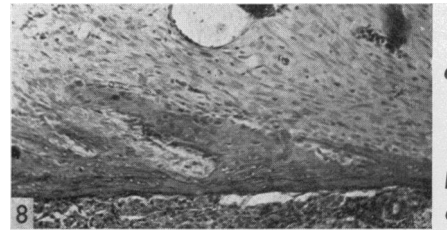

Figs. 1–8.

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EXPLANATION OF PLATE

The sections are all of the upper incisor teeth or of the alveolar bone surrounding them. Magnification × 106.

Figs. 1 and 2. Lingual alveolar bone in the neighbourhood of the naso-lacrimal duct. *a*, periodontal membrane; *b*, lingual alveolar bone; *c*, epithelium lining the naso-lacrimal duct. Fig. 1 from control rat 1245, Fig. 2 from rat 1239, which died after 10 days' hypervitaminosis A. Note the thinning and fragmentation of the bone in Fig. 2.

Figs. 3 and 4. The fundic bone and adjacent tissues. *a*, pulp; *b*, odontogenic organ; *c*, periodontal membrane; *d*, fundic bone; *e*, mucous gland. Fig. 3 from control rat 4243. Fig. 4 from rat 1238 after 13 days' hypervitaminosis A. Note the very narrow fundic bone in Fig. 4, and the many cement lines.

Figs. 5 and 6. Labial dentin of the upper incisor tooth stained by Gömöri's method of silver impregnation (1937). *a*, pre-experimental dentin; *b*, experimental dentin, separated by a zone taking the silver less well. Fig. 5 from control rat 1244. Fig. 6 from rat 1242 after 13 days' hypervitaminosis A. Note the prominent fibrils in Fig. 6, especially in the most recently formed dentin.

Fig. 7. Labial alveolar bone of rat 4213 after 54 days' avitaminosis A. *a*, alveolar bone; *b*, periodontal membrane; *c*, enamel organ. Note the wide layer of new bone, bordered with osteoblasts, laid down on the periodontal side of the alveolar bone, separated from the old bone by a reversal line.

Fig. 8. Fundic bone region, from rat 3617, which received $\frac{1}{3}$ i.u. vitamin A for 50 days. *a*, peric dontal membrane; *b*, fundic bone; *c*, mucous gland. Note the overgrowth of fundic bone into the periodontal membrane. The original size of the fundic bone can be seen outlined by a cement line (cf. Fig. 3).