TRANSPLANTATION OF TOOTH GERM ELEMENTS AND THE EXPERIMENTAL HETEROTOPIC FORMATION OF DENTIN AND ENAMEL*

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PLATES 9 TO 12

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The histologic proximity of epithelium to such superficial appendages of the organism as the scales, shell, hair, nails and the developing tooth has been discovered within the last century. Moreover, experiments in recent years (2–4) have shown that the epithelium of certain organs in mammals, notably the gall bladder and the urinary tract distal to the kidney, when transposed to certain connective tissue areas regularly causes the formation of osteoblasts and bone in these loci. Since the relationship of the calcified elements of the tooth to epithelium in the developmental stage is strikingly similar to bone forming after epithelial transplantation, and since the inorganic crystallites of teeth and bone are chemically identical even to X-ray diffraction studies (5, 6), it was considered advisable to investigate the odontogenic properties of tooth germ elements in an attempt to induce the extra-oral formation of dentin and enamel. The relatively common heterotopic occurrence of teeth in pathological situations, as in the pituitary (7) and elsewhere, especially in the ovary, as a result of teratomatous tumor formation lent support to the conception that this could be accomplished experimentally.

The idea of the ontogenetic relationship of epithelium to the developing tooth arose mostly as a result of the anatomical studies of Kölliker. Hertwig (8) de-

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scribed the penetration of the jaws by an epithelial sheath, which he believed was essential to tooth formation. The discovery of Tomes (9) that the epithelial enamel organ was present in the armadillo, whose peg-like teeth consist solely of dentin devoid of enamel, and the studies of von Brunn (10, 11), who showed that the entire tooth of rodents is surrounded at some time by the enamel organ, although the dorsal surface of the tooth is composed of dentin and only the ventral surface is covered by enamel, led to the belief that epithelium was necessary in some way for the development of both enamel and dentin. To quote von Brunn: "where there is no epithelial sheath, there can be no odontoblast formation and consequently no dentin," (11).[1]

In the present experiments the technique consisted in the autogenous transplantation of tooth germ elements to the connective tissues of the abdominal wall of young pups; so far as we could discover, this method has not been previously reported. Legros and Magitot (12), however, studied transplanted tooth germ elements in the much more difficult field of homogenous and heterogenous grafting. Their results achieved in the pre-aseptic era are noteworthy. These investigators removed dental follicles from young pups immediately after death and transplanted them subcutaneously into guinea pigs or older dogs. The heterogenous grafts were all lost through suppuration or resorption as were most of the homogenous grafts. The positive results obtained were as follows: 7 of 26 homogenous grafts of the complete dental follicle survived and led to regular development, and in 3 of 16 cases in which the pulp was removed and transplanted alone, the tissue survived and reproduced a new cap of dentin.

Methods

Young dogs between the ages of 3 and 6 weeks were used and all operations were done under ether anesthesia. An aseptic manner of operating in the mouth was impossible to attain and was found not necessary; the grafts were extraordinarily free from infection. The instruments used in the mouth were sterilized by heat, the operative field was swabbed with iodine and after isolation of the dental follicle, the tissues were removed with fresh instruments into sterile Ringer's solution. The abdominal operation was then done with asepsis.

The material grafted consisted in the soft tissues of the unerupted permanent canine tooth which was selected because of its large size and ease of accessibility. The canine tooth in the upper jaw was always found anterior and superior to the root of its deciduous precursor; to remove this tooth a 2.5 cm. incision was made

[1] Von Brunn (11), page 145.

in the gingiva covering the lateral aspects of the superior maxilla parallel to the root of the temporary canine tooth, down to the bone; the periosteum was reflected and the thin plate of bone overlying the tooth removed with a chisel. With care the tooth and its membranes were removed intact. Removal of the tooth in the mandible was slightly more difficult; after making parallel incisions in the gum margin, medial and lateral to the temporary teeth, the periosteum was reflected from the mandible, and a wedge-shaped piece of bone was sawed away just posterior to the deciduous canine, exposing the permanent tooth in the medial aspect of the mandible. Wounds in the jaw were not sutured.

The dental follicles were opened and the calcified cone of dentin and enamel was always discarded. In a number of cases, an X-ray photograph of the soft tissue was made before transplantation, and in all cases some tissue was excised from the graft for histological control. It was regularly possible to cleanly remove the pulp with its odontoblast layer from the dentin without adherent calcified particles, but it was much more difficult to dissociate calcified enamel from the ameloblast layer, and in many cases a few small bundles of preformed enamel were transplanted inadvertently with the epithelial layer.

The abdominal site for reception of the transplant was prepared by making a 2 cm. incision in the skin and external oblique muscle. The grafts were inserted between the internal and external oblique muscles, and the latter was then sutured as well as the skin with fine silk.

The animals were kept from 2 to 56 days on a stock diet of meat scraps, bread and lettuce, with an unlimited supply of cow's milk. A special group in which the known vitamin content of the food was maintained at a high level was fed in addition by daily gavage a supplementary ration consisting of butter 12 gm., tomato juice 12 cc., fresh yeast 4 gm., irradiated ergosterol (1000 D) 2 drops.

The soft tissues of the developing tooth at this stage consist of (*a*) the pale white pulp with odontoblasts on the surface and (*b*) the red epithelial layer consisting of an innermost cylindrical cell layer, the ameloblasts; next a cuboidal row of cells, the stratum intermedium; and outermost a thin layer of flattened epithelium surrounded by connective tissue with a rich vascular supply. The odontoblast-pulp membrane is joined at its base, where the blood vessels and nerves enter, with the more embryonic portion of the epithelial layer, the epithelial sheath of Hertwig, precursor of the tooth root. The membranes are separated normally by the more or less calcified tooth shell of dentin and enamel which in these experiments was always removed and discarded. The relationship of these membranes in the graft was, as will be shown, a determining factor in the product of the transplantation. The membranes were transplanted in various combinations and the distinct difference in color made for the ease of anatomical separation. First, the membranes were cut across so that the epithelial layer (Method A) and the pulp-odontoblast layer (Method B) could be transplanted to different parts of the abdominal wall. Secondly, the membranes were transplanted together (Method C) so that the epithelial layer had a quasi-normal relationship to the

pulp and the cylindrical ameloblasts were in close proximity to the odontoblasts; and in another series the epithelial layer instead of ensheathing the pulp was drawn upwards so that these membranes were in continuity but not approximated (Method D). Thus in the experiments done using Method D the epithelial layer bore a "skin-the-rabbit" relationship to the pulp. In another series (Method E) a transverse section of the pulp was circumcised so that all of the odontoblasts were removed together with a thin layer of underlying pulp cells; thus the surface cells of the pulp were transplanted to a different location from that of the central pulp cells. In Method F, a sheet of mouth epithelium covering the mandible was excised and transplanted to the abdominal wall.

RESULTS

Since great variations resulted depending on the nature and relationships of the material used for transplantation, the 6 series of experiments will be separately described. The infrequency of inflammation around the grafts, was noteworthy in view of the impossibility of maintaining complete asepsis in securing the grafts.

Method A. Isolation of the Epithelial Layer and Transplantation to the Abdominal Wall

Twenty-one experiments were done in this group; an animal was killed every 2nd day from 2 to 30 days after transplantation. It was somewhat difficult to remove the epithelium from the enamel without obtaining a few adherent enamel bundles. The preformed enamel bundles usually were small and regular, and the enamel rods relatively long and in microscopic section had a straight regular edge making it easy to differentiate transplanted from newly formed enamel.

These enamel bundles did not excite a specific response in the tissues; giant cells were completely lacking around them although present in great numbers around fortuitously adjacent silk fibres; the bundles uniformly became encapsulated by fibrous tissue or epithelium and the enamel rods appeared to be histogenetically inert.

The most significant features of the experiment were the total disappearance of the cylindrical ameloblasts, the absence of new enamel formation and failure of the epithelium to form cysts.

The epithelium survived only as a stratified epithelium composed in part of squamous cells and in part basal cells. As early as the 2nd day after transplantation, the cylindrical character of the ameloblasts was lost and the epithelium was forming islands and cords of cells which persisted. In the later stages, it was seen that some of the islands were composed entirely of basal cells, and others almost exclusively of stratified squamous cells. At 4 days, expansion of the epithelium

was easily observed, already more extensive than it becomes normally in the jaws. Mitotic figures were numerous. In later stages epithelial pearl formation was not unusual. It was of interest to observe the relationship of the basal to the squamous cells; in the largest islands, composed chiefly of basal cells, the center sometimes contained squamous cells, as if the basal form was dependent on a more favorable vascular relationship. Some of the epithelial islands surrounded connective tissue, so that in the plane of the section, the fibroblasts were completely encompassed.

There was no new formation of enamel detectable in any of the sections.

The epithelium showed no tendency to form cysts, except the small obviously necrotic centers of some large squamous cell islands, containing epithelial cells, whose nuclei almost filled them. This is an exceedingly unusual happening in epithelium under these conditions of subcutaneous transplantation.

Method B. Transplantation of the Isolated Odontoblast-Pulp Layer

As compared with the epithelial layer, it was easy to regularly remove the pulp with its surrounding odontoblasts from the dentin cap without any adherent traces of calcified material; this was repeatedly demonstrated by X-ray examination as well as by biopsy of random areas before transplantation, for histological examination. Twenty-four experiments were done in which this material was transported to the connective tissue areas of the abdominal wall or thigh. The results were similar, but the ease of identification of the tissue in the abdomen, as well as the absence of calcified elements in this site normally, made this location more satisfactory for the purposes of the experiment.

The duration of the experiment was from 1 to 26 days. In 12 of the experiments, exclusively those between 14 and 26 days, small masses of calcified dentin were found. Further proof that the dentin found in the later experiments was newly formed in the heterotopic location occurred in the observation that no dentin was found in any of the experiments before the 14th day.

In the material recovered for examination between the 2nd and 10th days, it was impossible to recognize the odontoblasts as such, but after this time aggregation of more densely staining compact cells associated with an eosinophilic protein secretion identified the future site of dentin formation. The pale staining stellate pulp cells with the included surviving empty preformed capillaries easily differentiated the transplant from the native abdominal connective tissue.

The calcified dentin occurred roughly at the junction of the pulp and the encapsulating fibroblasts. The dentin was found in circular, or irregular plaque form with collections of odontoblasts located almost exclusively on one surface and the other surfaces were encapsulated by common connective tissue. The

circular masses of dentin in places appeared just within the interior of the pulp. They were always surrounded by odontoblasts, usually both on the surface and in the interior. These masses of dentin had well defined canaliculi, resembling the tubules of normal dentin. By the 15th day the dentin was always calcified, but as late as the 26th day there was always an uncalcified zone separating it from the odontoblasts.

Some of the dentin enclosed living cells as if it had been secreted around fibroblasts which were thus included; in other places the interstitial cells closely resembled bone corpuscles. There was observed every gradation between true dentin, through osteodentin to true bone. As studies of the teeth in vitamin A and C deficiency (14, 15) have established, there is a close relationship between the cells known as odontoblasts and osteoblasts; and these observations were fully confirmed by the present experiment.

Method C. Transplantation of Odontoblast-Pulp and Epithelial Layers So That a Quasi-Normal Relationship Obtained

This experiment was done 6 times. The results were identical in each case although the duration of growth varied from 21 to 31 days after transplantation. The interesting features observed were the preservation of the cylindrical character of the ameloblasts and the formation of new enamel in normal relationship to these cells and to newly formed dentin.

The ameloblast and odontoblast layers survived the transplantation and produced a relatively large amount of the calcified tooth substances, enamel adjacent to the ameloblasts, and dentin close to the odontoblasts. Relatively long stretches of enamel epithelium and of enamel were found; the outline of the row of enamel rods was irregular and wavy, the enamel rods were short, and thus there were distinct differences between the newly formed enamel and the irregular narrow but long bundles with straight edges which characterized preformed transplanted enamel. Moreover enamel formed before the transplantation had no regular relationship to dentin such as existed here. In each case Hertwig's sheath was found, showing that this still undeveloped embryonal tissue is capable of survival in a new location. The growth of the epithelial and odontoblast layers was not entirely regular, in places these layers invaginated the pulp so that a shelf-like arrangement of dentin and enamel appeared in the pulp. The growth of the cell layers was not perfectly symmetrical, so that in some areas either layer was lacking. In the regions where ameloblasts were missing, the odontoblasts proliferated to form large irregular masses of dentin and small spheroidal denticles. In the

absence of the odontoblast layer, however, the cylindrical ameloblasts did not persist and were replaced by stratified squamous degeneration of the epithelium without formation of enamel rods. Thus enamel was only deposited on dentin, although dentin formation was definitely independent of enamel production, and the enamel rods formed only in association with cylindrical cells.

Method D. Transplantation of Epithelial and Odontoblast-Pulp Layers Together without Preservation of Normal Proximal Relationship of the Membranes

Twelve experiments were done using these membranes attached at the base of the follicle but with a deliberate attempt to avoid contact of the cylindrical ameloblasts with odontoblasts. The duration of the experiments varied from 9 to 56 days. The results can be interpreted as a combination of the results obtained by use of Methods A and B. At 9 days there was found early uncalcified dentin in the region of the pulp and masses of basal and squamous cell epithelium away from it. In 2 of the experiments the epithelial sheath of Hertwig was identified but cylindrical ameloblasts were not observed and there was no evidence of newly formed enamel. The only observable difference in the dentin formation was an apparent increase in the amount of dentin formed. The largest amount of dentin including cellular dentin and bone observed in these experiments occurred in these sections. As mentioned under Method A, in transplantation of the epithelial layer a few bundles of preformed enamel usually adhere to the epithelium, and in the present experiment not infrequently there were found masses of these preformed enamel rods entirely encapsulated by dentin. This is, of course, proof of the new formation of dentin in the abdominal wall. In certain areas, here as in Method B, there were observed irregular serpiginously contorted masses of dentin formed presumably as a result of the opportunity of the pulp to undergo free growth for a limited period.

Method E. Transplantation of the Center of Pulp to the Abdominal Wall as Compared with the Peripheral Portion Containing the Odontoblasts

In this experiment, the center of the pulp was completely freed from the odontoblasts, by a circumcision of the periphery. A 4 mm. transverse section was cut equatorially through the pulp, which was then pinned to a block of wood with

needles, allowing the surface layer of odontoblasts to be easily and completely excised with a razor. Each of the 2 masses of tissue consisting of the center and periphery of the pulp was transplanted to separate portions of the abdominal wall.

In 5 experiments with the center of the pulp, the tissue was recovered at 20, 24 and 29 days; the stellate pulp cells were easily seen, but there was no trace of dentin or calcified material found.

In 5 similar experiments with the surface layer of odontoblasts and necessarily the immediately subjacent pulp cells, the duration of the experiment being the same, small islands of dentin, with odontoblasts arranged along one surface were found in 4; in the 5th experiment, terminated at 29 days, no calcified tissue could be identified.

Method F. Transplantation of Gingival Epithelium to the Abdominal Wall

The gum was painted with iodine, in 7 experiments, and a thin layer of epithelium covering the lateral aspect of the mandible excised and transplanted to the abdominal wall. The graft survived 32, 47 and 69 days. In all cases there was infection, and in 2 experiments no epithelium could be identified at the termination of the experiment.

In brief, the epithelium survived, proliferated to form a cyst lined with squamous epithelium and produced no calcified dental substance. The basal papillae of the original epithelium survived, but the newly formed portion of the cyst did not reproduce this papillary pattern but persisted in the form of a flat stratified squamous cell layer. A leucocytic invasion surrounded the epithelium in all cases.

DISCUSSION

Aside from the actual heterotopic formation of dentin and enamel the most interesting feature of these experiments was the epithelial cytomorphosis. It seems clear from the histological evidence that when the enamel epithelium is associated in an approximately normal relationship to the odontoblasts and pulp, the cylindrical character of the ameloblasts is preserved with the production of new enamel rods and that otherwise these properties are lost. The maintenance of the form of the epithelium and its function in producing enamel seems to be due to the influence of the mesodermic tissue on the epithelial

ameloblasts themselves, and if so this is a converse situation to the effect of epithelium such as that lining the lower urinary tract on certain strains of fibroblasts causing them to change form and function in the production of bone. This mutual interrelationship of supporting tissues and epithelium on each other in the postnatal state, whereby changes in the one or the other are reflected in pronounced anatomical and physiological variations in the tissue, is of great interest and is being further studied in this laboratory.

The inability of the epithelium to form cysts, excluding the pseudocysts in large degenerating squamous islands, is likewise a most remarkable property of transplanted epithelium and in this respect this epithelium is unique in our experience with normal epithelia. The absence of cyst formation in this stratified baso-squamous epithelium at once calls to mind the islands of epithelium normally occurring in the periodontal membrane of all animals after the tooth has erupted above the gingival margin. This epithelium first described by Malassez (13) likewise shows no tendency to cyst formation under normal conditions and the appearance of the enamel organ when its normal relationship to the pulp is lost through transplanting is quite similar to the *débris épithéliaux paradentaire*.

It may be of interest to return briefly to our original thesis and to discuss the influence of epithelium on the formation of calcified tooth elements and to the similarity of this process to the ossification-inducing action of the epithelium as above mentioned. It is certain that for every developing tooth, there is in the closest relationship an epithelial downgrowth from the oral cavity. The hypothesis of von Brunn, since accepted by many investigators, was that no calcified tooth elements can be built without this epithelial ingrowth, and that epithelium stimulates the maxillary connective tissues to form odontoblasts and thus dentin. There thus appears a similarity to the osteogenic influence of bone-stimulating epithelia on fibroblasts. The present experiments, however, indicate that the view of von Brunn quoted above that "where there is no epithelial sheath, there can be no odontoblast formation and consequently no dentin" needs modification, in that odontoblasts, which have arisen as a result of epithelial influence on connective tissue, do not further need for their function the presence of epithelium. The evidence shows that the odontoblasts

arose as a result of the action of epithelium on the maxillary mesenchyme, causing a permanent change in these cells. These transplanted odontoblasts then were capable of forming dentin in the abdominal wall without further aid from the epithelium. The epithelial influence on the fibroblasts thus has a local hereditary influence as far as these cells are concerned, both in their form and function, which is precisely what occurs with the osteogenic epithelia. Unpublished experiments have clearly shown in this laboratory that the bone-forming properties induced in fibroblasts by epithelial stimulation are thereafter inherited; bone formed from transplantation of urinary bladder epithelium to the abdominal wall was later freed from the epithelium, was fractured and promptly the break healed by bony union, through the inheritance of the osteogenic character in the daughter cells of the original fibroblasts that had formed bone, although the original epithelial osteogenic stimulus had been removed.

An obvious difference between the present experiments and the osteogenic stimulus of epithelium on fibroblasts, in that enamel epithelium did not stimulate the abdominal wall fibroblasts to form calcified elements, may perhaps be best explained by the fact that in the absence of the mesodermic pulp elements, the enamel organ loses its specialized form and degenerates in the direction of gingival epithelium.

It is hoped that the development of a method whereby the calcified components of the tooth are formed in a bacteriologically sterile site such as the abdominal wall will provide new means for study both of kataplastic process such as dental decay under aseptic conditions in the absence of saliva, as well as the histogenic details and physiology of the early formative stages of the calcified tooth elements.

SUMMARY

The formation of dentin and enamel in the abdominal wall in young pups was achieved by transplantation of the soft tissues of the developing tooth germ. An interesting finding was the cytomorphosis of the epithelium of the enamel organ. When this was transplanted so that the ameloblasts were in contact with the odontoblasts the cylindrical character of the epithelial cells was preserved and enamel was produced; otherwise the cylindrical shape of these cells was lost and a stratified epithelium resulted, resembling the gingival and certain

tumors (the adamantinoma) of the jaw and related structures. This degenerated epithelium did not produce enamel and had an important characteristic of not forming cysts in a closed connective tissue space, instead forming islands and cords of cells with epithelial pearl formation. Thus the influence of mesodermic connective tissue derivatives on the form and function of epithelium is presented. The odontoblasts were found capable of survival as such and readily formed new dentin in transplantation; the stellate cells of the pulp were inert from the standpoint of inducing calcification.

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EXPLANATION OF PLATES

The tissue from which these photomicrographs were made was prepared by formalin fixation, dehydration and paraffin impregnation. The tissue shown in Figs. 6 to 12, in addition, was decalcified in 5 per cent nitric acid. All sections were stained with hematoxylin and eosin.

PLATE 9

FIG. 1. Transplantation of enamel epithelium to abdominal wall (Method A), 4 days. The cylindrical character of the ameloblasts is now represented only by spindle-shaped cells; most of the epithelium has assumed a stratified squamous form. ×145.

FIG. 2. The same as Fig. 1, 17 days. The enamel epithelium has survived as islands formed chiefly of basal cells. ×160.

FIG. 3. The same as Fig. 1, 21 days. Two islands of epithelium (*A*, *A'*) are shown, with an epithelial cord at *B*. ×145.

FIG. 4. The same as Fig. 1, 16 days. A large epithelial island with many squamous cells is shown. ×115.

PLATE 10

FIG. 5. Transplantation of odontoblast-pulp membrane to abdominal wall (Method B), 14 days. At the junction of the pulp (*P*) with the abdominal connective tissue cells (*F*) there is an island of early dentin, only slightly calcified; odontoblasts may be seen at *O*. ×145.

FIG. 6. The same as Fig. 5, 24 days. At the interface between pulp (*P*) and connective tissue (*F*), a large island of dentin has formed; odontoblasts (*O*) are seen on one surface. ×140.

FIG. 7. The same as Fig. 5, 21 days. A serpiginous mass of dentin has formed at the junction of the pulp (*P*) and the encapsulating fibroblasts (*F*). ×145.

FIG. 8. The same as Fig. 5, 28 days. Five oval and circular masses of dentin, and a plaque form are seen at the junction of pulp (*P*) and connective tissue (*F*). Note the odontoblasts on the surface of the denticles. ×115.

PLATE 11

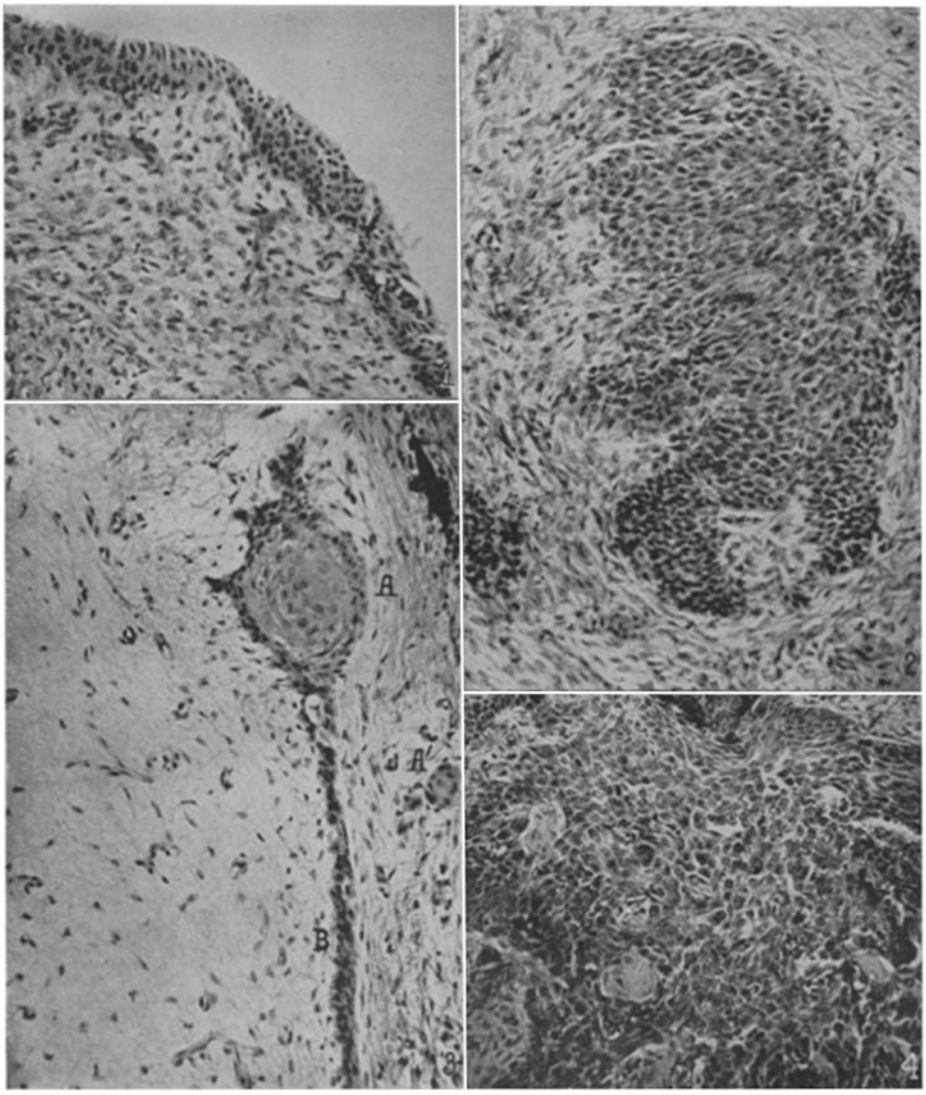
FIG. 9. Transplantation of epithelial and pulp odontoblast layers together, but not in contact (Method D), 28 days. A large mass of slightly cellular dentin has formed. ×215.

FIG. 10. Transplantation of epithelial and mesodermic layers together, with the ameloblasts in intimate contact with the odontoblasts (Method C), 20 days. Note Hertwig's sheath (*H*), newly formed dentin and enamel (*E*), squamous degeneration of epithelium (*D*). ×26.

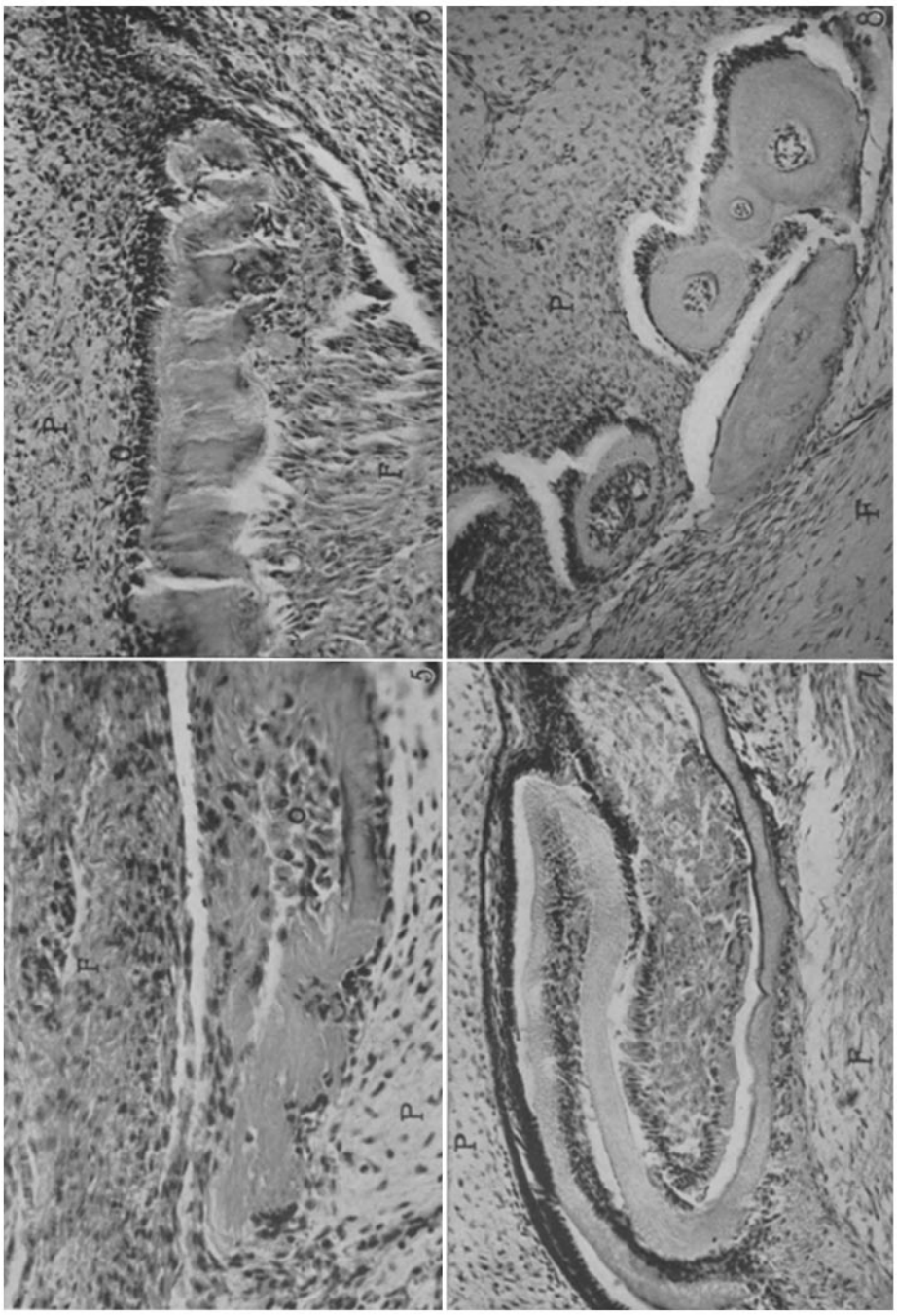
PLATE 12

FIG. 11. The same as Fig. 10, 21 days. The pulp (*P*) with its odontoblasts (*O*) may be seen separated by a new formation of dentin and enamel from the cylindrical ameloblasts (*A*). The surrounding connective tissue of the abdominal wall is seen at *F*. ×370.

FIG. 12. The same as Fig. 10, 26 days. A somewhat tangential section of dentin (*D*) and enamel (*E*) to show the hexagonal enamel prisms. The ameloblast layer is seen at *A*. ×405.



(Huggins *et al.*: Transplantation of tooth germ elements)



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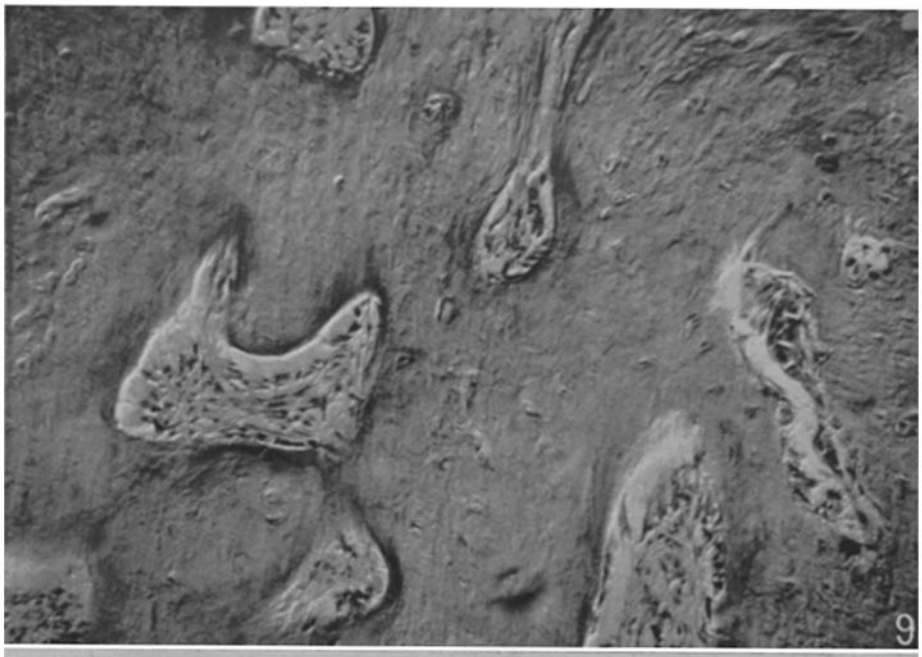

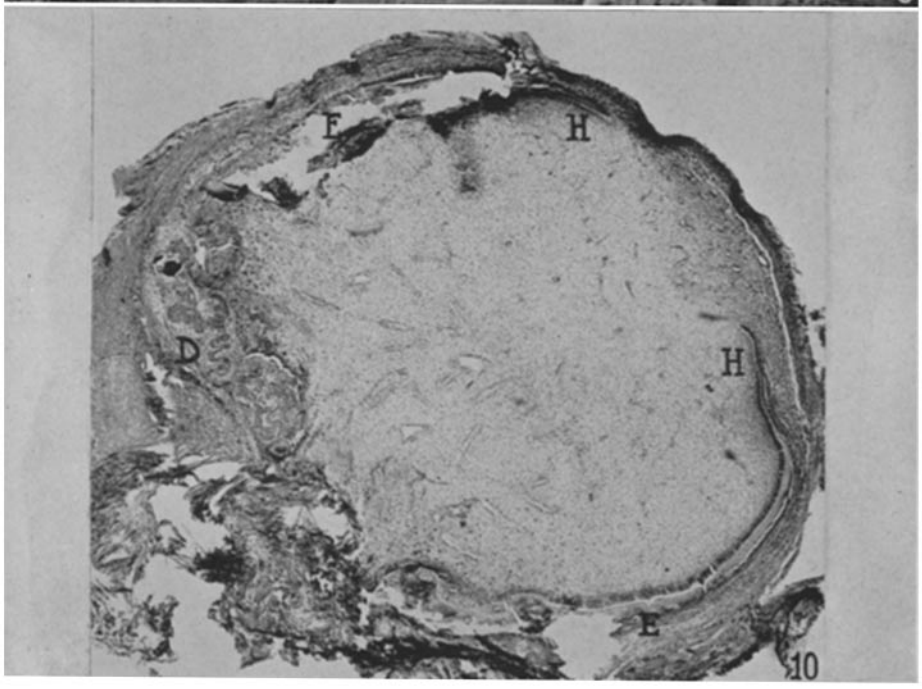

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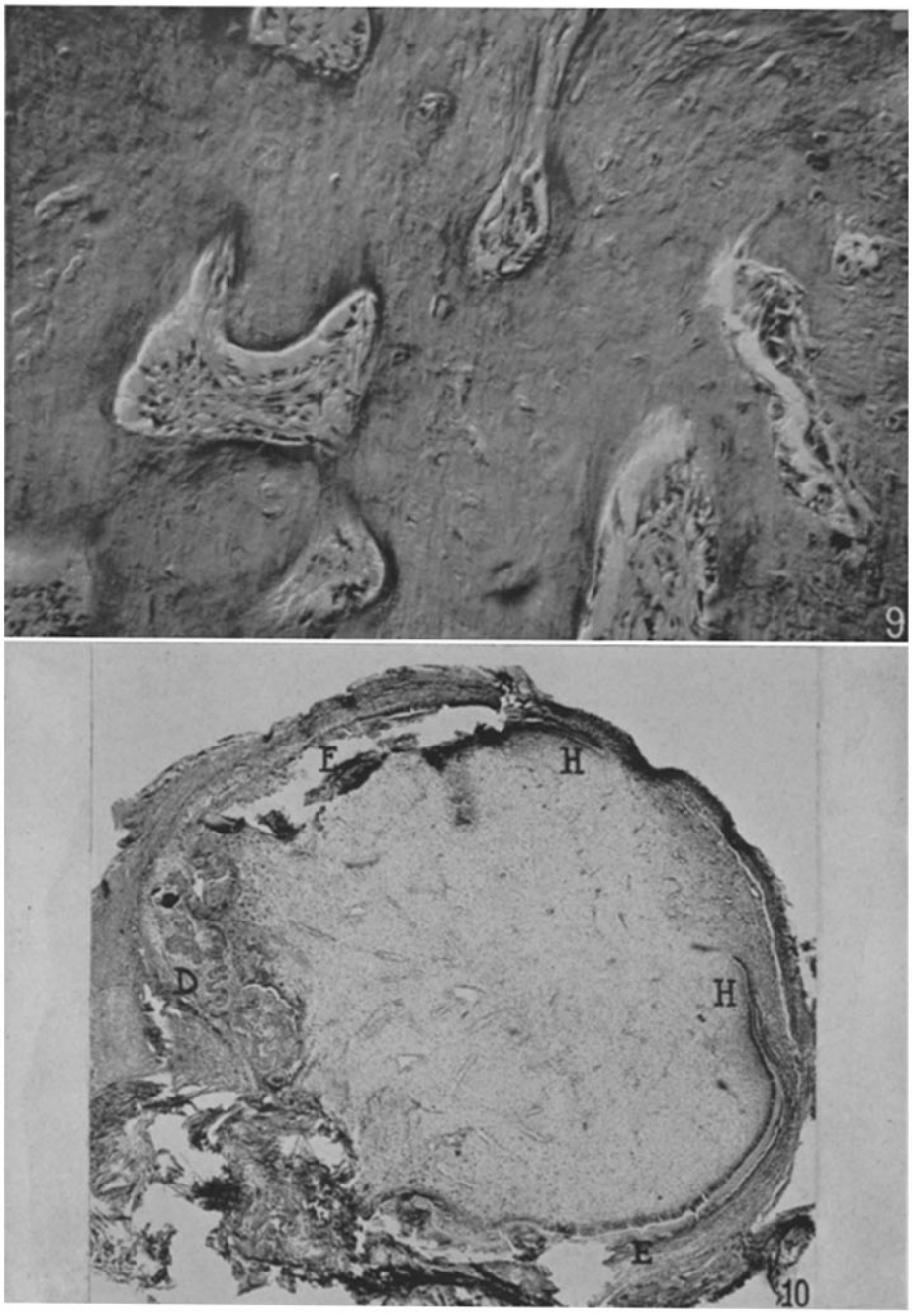

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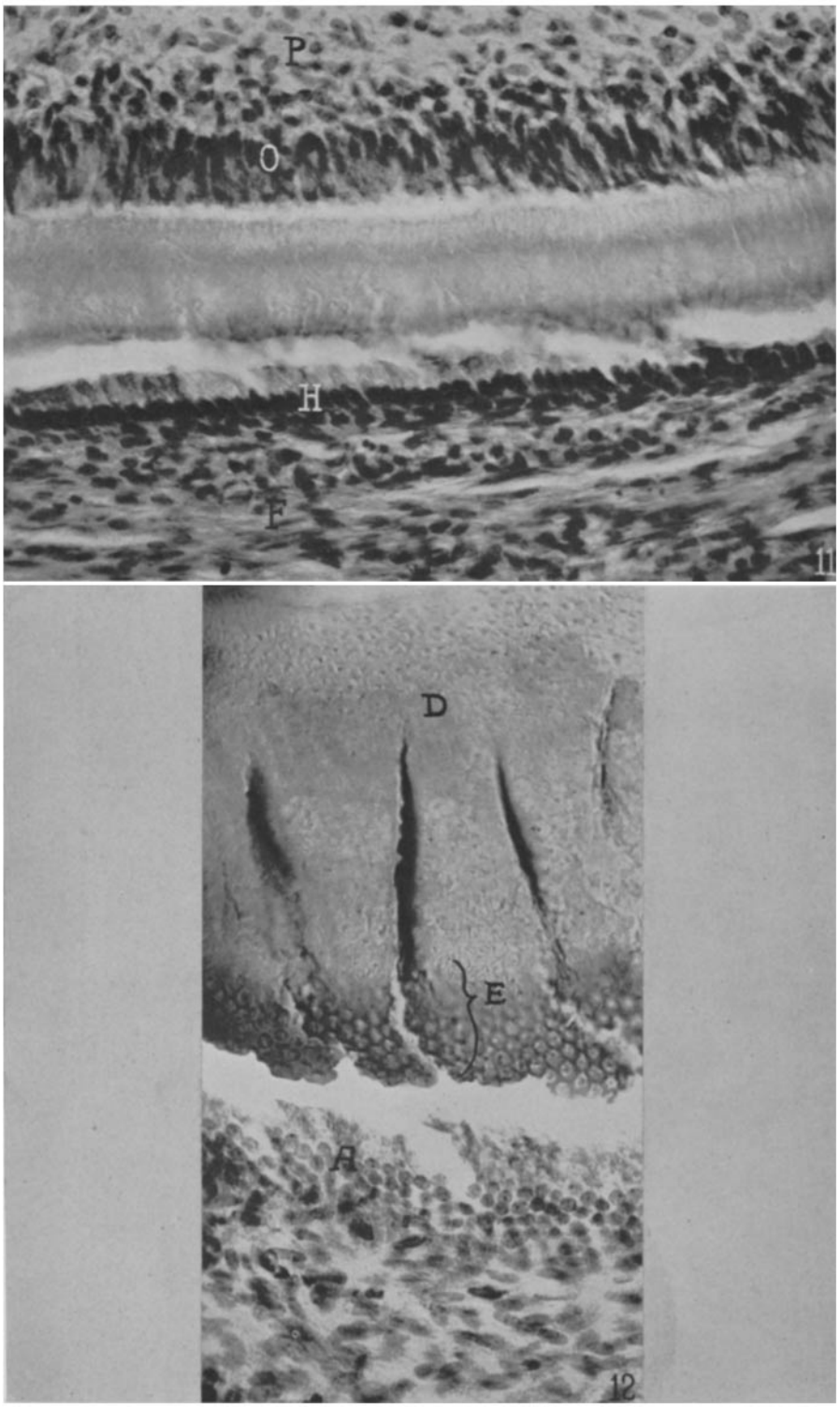

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