Osteogenesis induced by homologous transplantation of dentine intracerebrally and subcutaneously into rats

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Hard tissue formation associated with dentine in an environment different from the dental pulp was studied by transplanting fragments of dentine between two successive litters of the same parents. The dentine was taken from the incisors of the three months old donor rats and transplanted intracerabrally or subpannicularly into 162 five days old hosts that were of the same sex as the donors. The hosts were killed after 2 to 540 days and 279 of the 324 inserted transplants recovered for histological study. The transplants were mostly found encapsulated. Cellular signs of inflammation were occasionally seen, even in long-term transplant capsules. Ependymal cell chords were found in close contact with the intracerebrally placed transplants and also at sites were bone-like tissue was present. Bone was present in conjunction with 81 transplants at 16 days or later; the majority of these were recovered from the brain tissue. The extent of bone formation varied considerably, and intact transplants were found even after 540 days. As a transplantation site the brain or the subpannicular tissue seem to differ from the dental pulp since it has been noted that intrapulpal fragments of dentine become surrounded by dentine whereas no such tissue developed in the present experiment.

Key-words: Dentine; osteogenesis; transplantation

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The present study was conducted in order to clarify the potentiality of ectopically transplanted dentine to induce hard tissue formation. In an experimental study on reactions of the dental pulp to trauma (*Luostarinen*, 1971) it was found that dentine splinters incidentally forced into the pulp tissue gradually became surrounded by osteodentin which was eventually followed by tubular pre- and secondary dentine. Dentine and decalcified dentinocemental matrix transplanted into osseous environments have been observed to induce bone formation (*Beube*, 1960; *Yeomans & Urist*, 1967; *Scopp et al.*, 1970). Divergent results have been reported from experiments of dentine transplantation into non-osseous sites. The subcutaneous transplantation of decalcified dentine was observed by *Huggins & Urist* (1970) to result in bone formation, whereas no bone was noted to have formed on non-decalcified or decalcified dentino-cemental chips (*Morris*, 1967), on decalcified dentin powder (*Huggins et al.*, 1970) or on decalcified rat molars (*Irving & Bond*, 1968) in the same transplantation site. Regarding the actual reason for the osteogenesis

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in such experiments there seem to be conflicting opinions and it has been suggested that the transplant environment is a primary factor in determining whether bone will form on transplants.

Since the brain tissue has been found to be a favourable transplantation site (*Willis*, 1935; *Crouse*, 1956; *Koski & Rönning*, 1966) it was thought that it could be used for studying whether dentine fragments, devoid of actual cells, possess dentinogenesis inducing potentials in an environment different from that of the pulp tissue. For comparison the subpannicular tissue was selected as a second transplantation site.

MATERIAL AND METHODS

About 200 Long-Evans rats were used in the experiment. Out of these 162 served as hosts and the rest as donors. The transplantation was done between two successive litters of the same parents. The dentine was taken from the three months old animals of the first litter and transplanted into animals of the second litter, five days old and of the same sex as the donor. Immediately after the killing of the donor the incisors were anteriorly freed of surrounding soft tissue and bone by means of a water cooled air jet bur. The enamel was cut away and the pulp tissue was scraped out of the opened pulp chamber. The dentine was cut to pieces with the longest dimension not exceeding 4 mm. Some pieces were fixed immediately for histologic checking of possible remnants of bone or pulpal cells; the rest of the pieces were pooled in physiologic saline for transplantation.

Each host received two fragments of dentine. One was transplanted into the brain tissue through a slit in the frontoparietal suture by means of a 10 gauge syringe needle having the mandril functioning as a plunger; the second piece was put under the superficial fascia of the back applying a method described earlier (*Felts*, 1959). The hosts were killed 2, 4, 8, 16, 32, 64, 128, 340, 460, and 540 days after the transplantation, from 12 to 20 on each day. The transplants that were found were fixed in formol-saline and decalcified; the 6 microns thick sections were stained with haematoxylin and eosin or with a polychrome stain (*Herovici*, 1963).

RESULTS

Generally the host animals seemed to thrive. Out of the 162 hosts eight died before the termination of the experiment. Some of the older animals appeared relatively small in size.

Of the original number of transplants, 324, that was equally divided between the two transplantation sites, 279 were recovered, 141 from the brain and 138 from the subpannicular tissue (Table 1). The intracerebral transplants were generally found free in the brain substance, some in a cavity filled with liquid, some in immediate contact with the neural mass; one was attached to the calvarium. Grossly the transplants seemed virtually unchanged as compared with the appearance at the insertation. The subpannicular transplants were as a rule attached to the superficial fascia and also these transplants appeared fairly unchanged. Signs of increased vascularization were observed around the subpannicular transplants already two days after the insertation; this feature did not essentially change with the age of the hosts. There were occasional signs of infection both in the brain and in the subpannicular tissue; in the brain there were large abscesses in three animals.

Table I. *Statistical data related to the experiment*

N	Days after transplantation										Total
	2	4	8	16	32	64	128	340	460	540	
Hosts originally	15	15	15	15	15	15	15	20	17	20	162
Hosts at day of transplant recovery	12	13	15	15	12	15	15	20	17	20	154
Recovered intracerebral transplants	12	13	12	15	12	13	14	18	15	17	141
Revocered subpannicular transplants	12	13	15	14	10	14	12	17	15	16	138
Intracerebral transplants with bone*	0	0	0	1	1	2	12	15	14	14	59
Subpannicular transplants with bone*	0	0	0	0	1	2	7	3	4	5	22

*Formations called »bone-like tissue» in the text are not included in the numbers

Histology

The histological study of 59 dentine fragments selected randomly out of the pooled pieces to be transplanted revealed that ten had some cells attached; in four of these there were traces of the pulp, while remnants of the periodontal membrane was seen on six pieces one of which carried some bone. Also some few of the transplants examined after recovery from the host animal had the abovementioned tissue remnants adherent; the pulp tissue then appeared necrotic and displayed no odontoblasts, the periodontal fibers were easily recognizable due to their distinct arrangement and the bone matrix was mature in character. On some recovered transplants there were traces of enamel that was covered by inflammatory cells and seemed to be in a state of decomposition.

The findings to be presented in the following represent the general microscopical picture of each examination day; the variation was greatest in the older animals. Since none or very little of the tissue surrounding the transplants was dissected out for histological study the account of the host tissue reactions will be sparse. Data pertaining to presence of bone in conjunction with the original transplant are presented in Table I.

Two days. Transplants were surrounded by a loose capsule. Around the intracerebral transplants the capsule was generally one cell layer thick or virtually missing, sometimes it was fibrous. The capsule around the subpannicular transplants was thicker, more continuous and fibrous than around the intracerebrally transplanted pieces of dentine; in both transplantation sites the fibres appeared collagenous in polarized light and in staining reactions. The peripheral part of the thicker capsulae was relatively poor in cells, closer to the dentine the capsular wall resembled loose connective tissue and, in immediate contact with particularly the subpannicularly transplanted dentine, there were round cells typical of acute

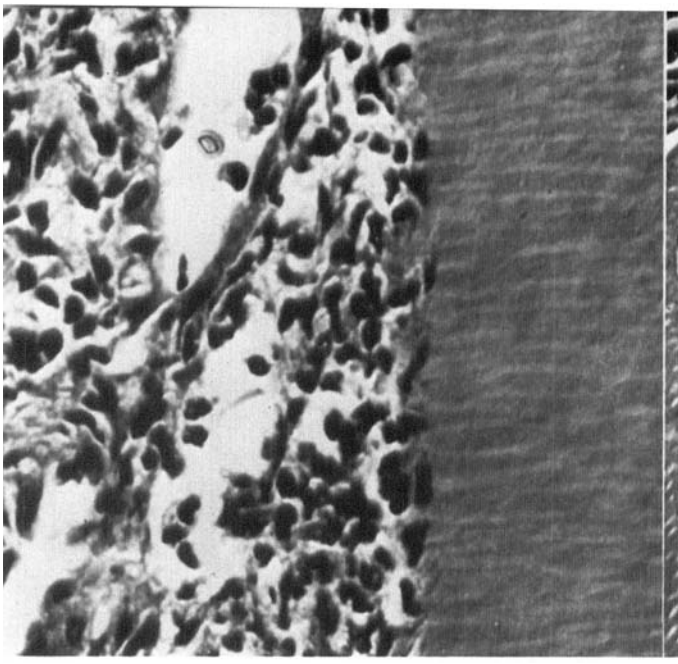

Fig. 1. Intracerebral dentine transplant that has been recovered two days after insertation. The surface of the dentine is slightly roughened and rounded cells occupy small excavations. Polychrome stain. × 450.

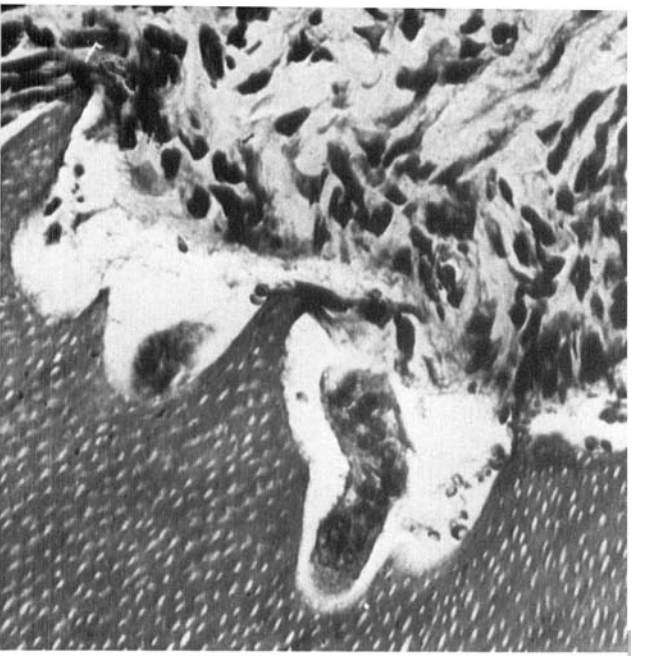

Fig. 2. Intracerebral dentine transplant that has been recovered 16 days after the insertation. The surface of the dentine displays deep lacunae with invading multinucleated cells. Polychrome stain. × 300.

inflammation (mainly polymorphonuclear granulocytes). Some surfaces of the dentine were rather even and intact whereas others displayed a slight blurring (roughness); in the latter case there were small rounded or ovoid cells occupying minor excavations in the surface (Fig. 1).

Four days. On the intracerebral transplants chords of ependymal cells were attached to the capsulae that generally were very thin and fragmentous although also capsulae with thick walls composed of loosely packed fibers were found. Subpannicularly the capsular walls were thicker and less loose in texture. Peripherally the capsular wall was relatively poor in vascularization whereas adjacent to the dentin it contained many capillaries. Frequently inflammatory cells occupied the space between the capsule and the actual transplant. As compared to the situation at two days the roughness of the dentin surfaces was more pronounced and there was a zone-like formation of non-cellular material between the original dentin and the cover of rounded cells. Small islands with staining properties resembling bone were incorporated in this irregular mass.

Eight days. Around and in contact with the intracerebral transplants there was an abundance of ependymal cell chords. The capsulae surrounding the subpannicular transplants were richly vascularized. In the previously non-cellular material found with some transplants there were now cells embedded which gave the structure the appearance of osseous tissue.

16, 32 and 64 days. The capsulae were still more massive and dense around the subpannicular transplants as compared to the intracerebral ones. However, at 16 days one intracerebral dentine transplant was surrounded by an exceptionally thick capsule inside of which there were also small islands of bone. Cell populations typical of acute inflammation were still seen at 16 days. Particularly the intracerebrally transplanted fragments of dentin displayed eroded lacunae contain-

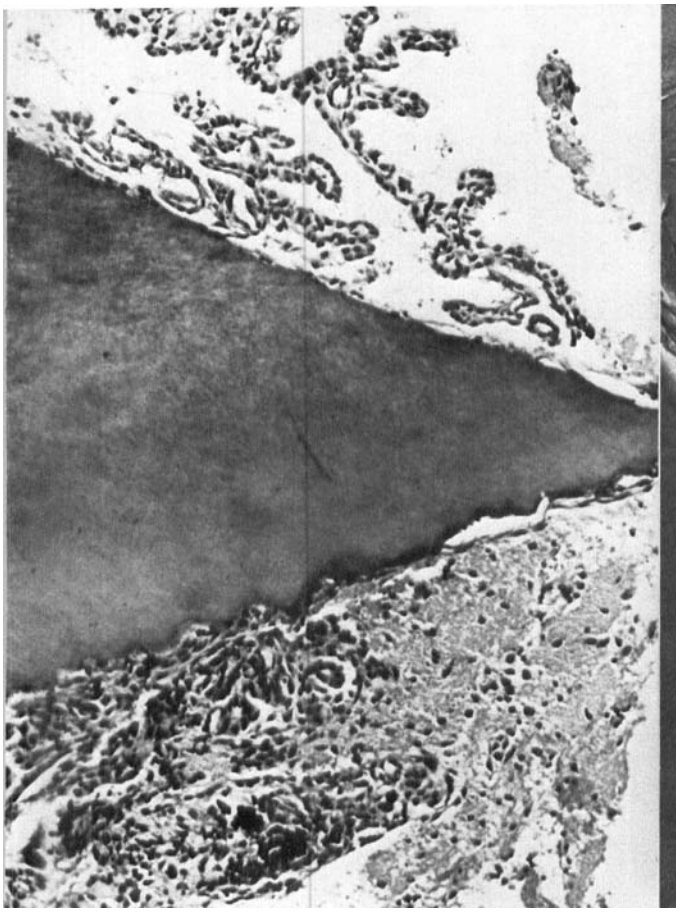

Fig. 3. Intracerebral dentine transplant that has been recovered 16 days after the insertation. Ependymal cells are in close contact with the transplant surface. Haematoxylin — eosin stain. × 45.

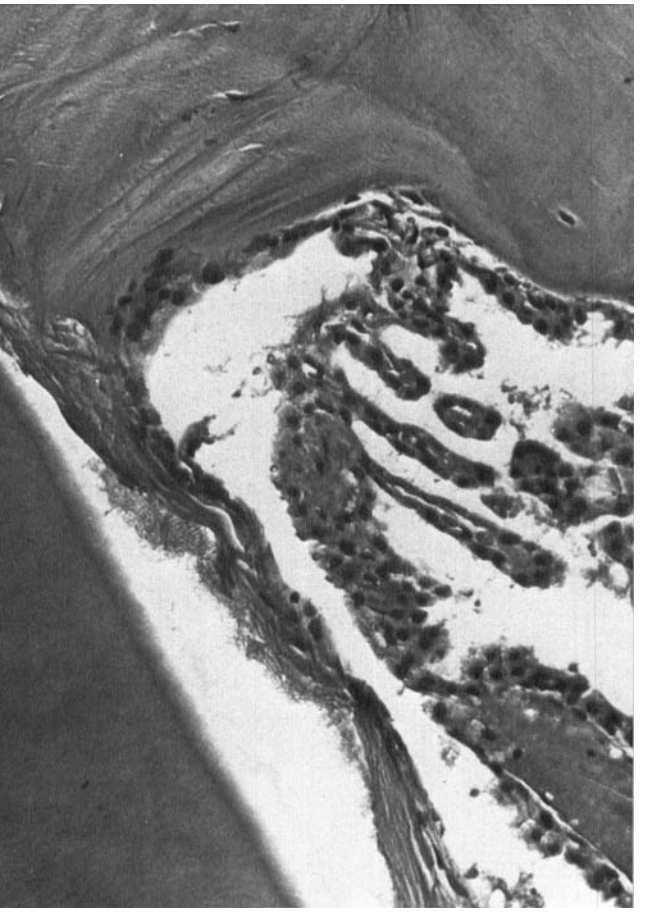

Fig. 4. Intracerebral dentine transplant that has been recovered 460 days after the insertation. The ependymal cell chords are lining the surface of the forming bone-like tissue. Polychrome stain. × 170.

ing multinucleated cells with a resemblance to osteoclasts (Fig. 2). Closely associated with the intracerebral transplants there were cyst-like structures the walls of which were composed of ependymal cells (Fig. 3 and 4). The lumen of these structures was filled with vacuolated aggregates of erythrocytes that seemed to be in a state of decomposition. These formations were found at all later observation days and sometimes adjoined bone-like tissue (Fig. 4).

128 days. Ependymal cells were not seen as frequently as earlier. Most of the intracerebral transplants were partly covered with lamellar bone that, due to numerous distinct resting lines, resembled cementum. Generally the bone embodied relatively few osteocytes. In some instances the bone merged without a clear border into the original transplant or the amorphous mass (cf. 8 days). The subpannicular transplants were still fairly intact or had an appendix of bone-resembling tissue. Also bone was found either in close contact with the dentine or at a distance from it.

340 days. Many of the intracerebral transplants were virtually surrounded by lamellar bone that appeared firmly attached to the dentine (Fig. 5). The subpannicular transplants displayed an increased amount of eroded surface although intact surfaces were also still seen. Bone and bone resembling tissue were found

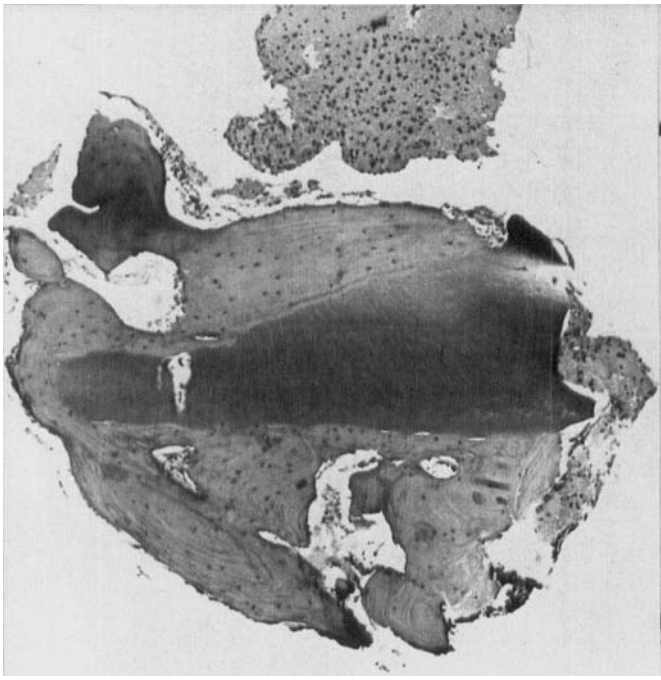

Fig. 5. Intracerebral dentine transplant is virtually surrounded by bone at recovery 340 after the insertation. Polychrome stain. × 38.

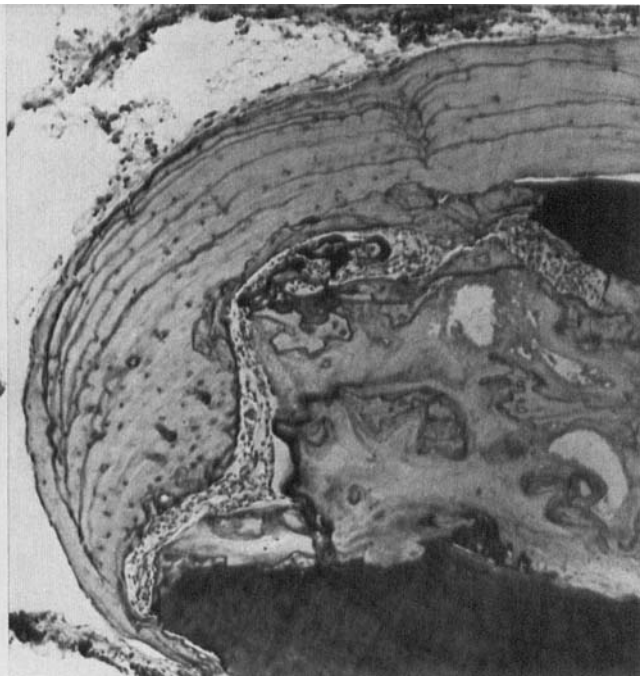

Fig. 6. Subpannicular dentine transplant with an appendix of lamellar bone at recovery 460 after insertation. Between the dentine and the bone there is an amorphous, almost non-cellular mass. Haematoxylin-eosin stain. × 38.

attached to the dentine; bony islands were also found somewhat remote from the dentine.

460 days. The appearance of the intracerebral transplants was not essentially changed when compared to 340 days. Inside the capsule of some subpannicular transplants cell populations typical of chronic inflammation were observed; these cells were located in small excavations of the dentine surface. However, the dentine also frequently appeared intact. Lamellar bone surrounded many of the subpannicular transplants (Fig. 6) but it was not always very well attached to the dentin inasmuch as ruptures were common. The osteocytes were large and rounded in some parts and more compact in other areas of the same transplant; also the number of osteocytes per square unit varied considerably.

540 days. Some intracerebral transplants were comparable in appearance with those recovered at 16 days, i.e. the capsule, partly composed of ependymal cells, enclosed the original transplant and the cell-containing amorphous mass but no bone. Subpannicularly there were still signs of chronic inflammation. On one intracerebral transplant the free surface of the amorphous material adjoining the original dentine was covered with tightly packed odontoblast-like cells. These cells were separated from bone resembling tissue by formations that had the appearance of acinous glandular secretory units (Fig. 7). Dentine formation, however, was not seen to have taken place here or on any earlier examination day. Inside the capsule of two intracerebral transplants (and one at 340 days) there were bizarre cluster-formations at a distance from the dentine. The clusters were surrounded by ovoid cells and they were divided by thin partitions into small, rounded compartments. Each separate compartment contained a generally non-cellular, possibly fibrous mass that was arranged in concentric, dif-

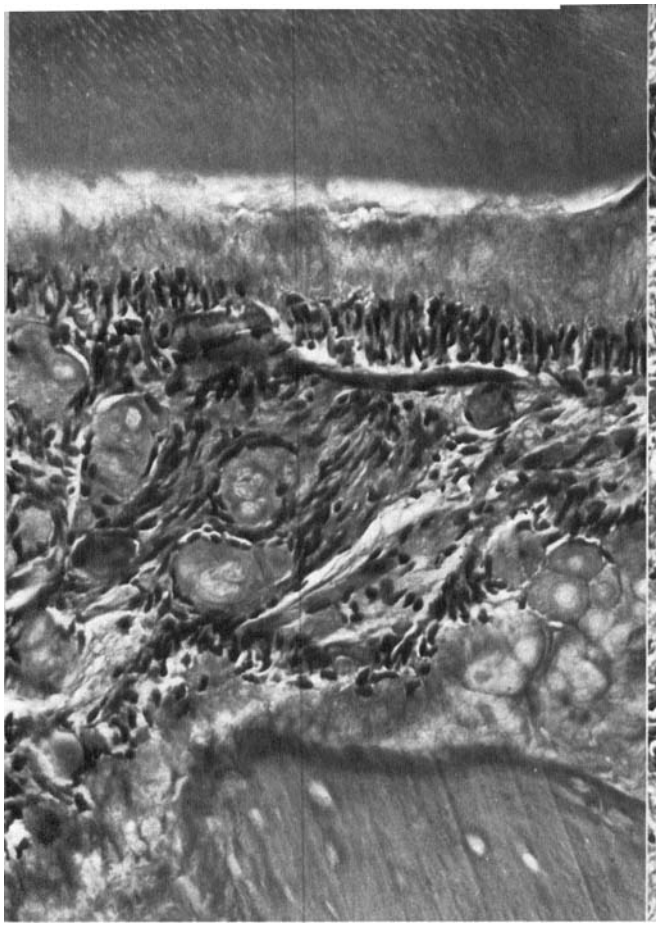

Fig. 7. Intracerebral dentine transplant recovered 540 days after the insertation. The uppermost cells closely resemble odontoblasts. Note the glandular appearance of the structure adjacent to the bone-like tissue. Polychrome stain. × 170.

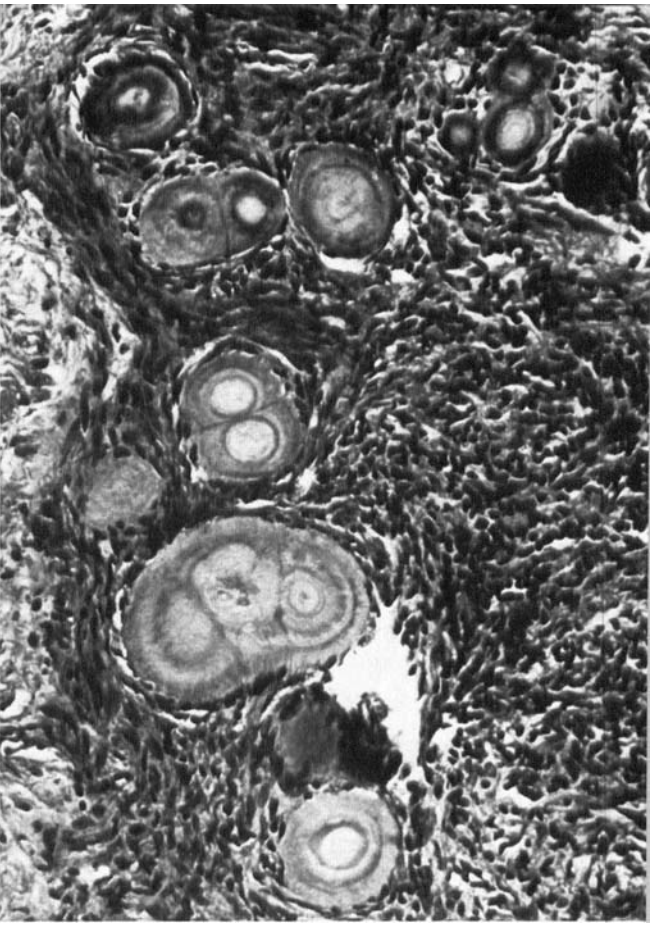

Fig. 8. In the vicinity of an intracerebral dentine transplant recovered 540 days after the insertation there are concentric bodies; the center of some of the formation is occupied by cells. Polychrome stain. × 170.

fuse zones the central point of which often was occupied by a single cell (Fig. 8). The concentric formations were birefringent in polarized light.

DISCUSSION

Actual dentinogenesis did not follow from the transplantation of dentine into the brain or the subpannicular tissue. Bone formation, however, was often evident and also other forms of differentiated connective tissue developed around the transplants in both transplantation sites.

Within some few days the transplants became surrounded by a capsule that subpannicularly always was fibrous and also intracerebrally there were frequently fibrous elements with features characteristic of collagen. Because the transplanted pieces of dentine were freed of adherent other tissues it is conceivable that these fibrous structures originated from the tissues surrounding the transplantation site, the brain or the subpannicular loose connective tissue. In the brain the structural components that primarily could be held responsible for the appearance of connective tissue elements are the microglia cells that possibly are of mesenchymal origin (cf. Ham, 1957). One is also reminded of the finding that embryonic neuroepithelium is able to secrete collagen within 1—2 days of *in vitro* cultivation (*Cohen & Hay*, 1971). At present no

definitive solution to this matter can be put forward.

The round cell infiltration that was observed inside the capsule of both intracerebral and subpannicular transplants was at first typical of acute inflammation; similar responses have been considered unrealated to the specific implanted tissue (*Irving & Bond*, 1968). Abscesses, as found around allogenically transplanted powdered, sterile dentine (*Huggins et al.*, 1970) occurred rarely in association with the present transplants although they were not prepared and handled aseptically. This diversity in reactions may be due to differences in particle size since it has been suggested from observations of bone transplantation that the inflammatory reaction is related to the amount of surface area of the transplant exposed to the host tissue (*Anderson et al.*, 1961). The histological picture of chronic inflammation that gradually became manifest may be considered an indication of a host reaction. However, these local signs of transplant rejection were in any case not very pronounced and, although dentine resorption associated with mono- or multinuclear cells was observed considerably earlier than in the experiment of *Irving & Bond* (1968), this was not any prominent feature. Thus the transplantation of dentine between two successive litters of the same parents seemed to render the transplants fairly compatible to the host tissue.

In the present experiment bone was detected around both intracerebrally and subpannicularly transplanted dentine. The bone varied in appearance from well organized lamellar bone to tissue poor in cells but with some morphological features and staining reactions characteristic of bone; the latter type of tissue has been reported by *Urist* (1971) to be found on transplanted enamel matrix. No actual bone marrow was observed to have developed in association with the present transplants whereas *Urist* (1971) and *Morris* (1972) found bony cavities containing bone marrow after transplantation of demineralized dentine.

The appearance of bone on the present transplants is at variance with the findings of *Huggins et al.* (1970) who did not notice any bone formation at all to have taken place after subcutaneous transplantation of mineralized dentine powder. The same authors reported bone to have formed within ten days after the transplantation of powdered demineralized dentine which is a considerably shorter post-operative timelaps than that required in the present experiment for bone to appear. However, with the passing of time (Table I) the transplants associated with bone became relatively numerous so that in the older hosts the majority of transplants (50—70 %) had some bone adjunct. *Barg & Urist* (1967) found that the ossification process on transplanted decalcified dentine matrix always was preceded by the appearance of excavation chambers caused by resorption which was retarded if undecalcified dentine was transplanted. The fact that some of the present transplants still at 540 days appeared virtually intact and without bone formation could be an expression of such a retardation. The latent period, however, seems unproportionally long and another explanation would be that these transplants could have been taken from the extreme incisal edge of the donor tooth that perhaps does not possess the same inductive properties as the matrix from the more vital posterior part.

As a transplantation site the pulp *per se* seems to possess properties different from the brain or the subpannicular tissue since *Luostarinen* (1971) noted that in-

trapulpal fragments of dentine, apparently devoid of cells, gradually became surrounded by dentine-like tissue whereas no such tissue developed here or after the subpannicular transplantation of pulps (*Zussman*, 1966). Cells resembling odontoblasts were observed only in association with one transplant. This was probably the result of unintentional transplantation of some pulp tissue since *Zussman* (1966) found the transplantation of pulps to eventually lead to the restoration of odontoblasts participating in bone formation. As far as osteogenesis is concerned it could thus be suspected that in the present experiment this has resulted from transplantation of donor cells that, according to the random check, could have been adherent to about 20% of the original transplants. This, however, is ruled out by the fact that after the longer post-operative intervals the majority of the transplants carried some bone.

As pointed out, the major part of the present transplants were presumably devoid of any cell bodies when inserted into the brain tissue by means of a syringe needle. Consequently the osteoblasts must have originated from the surrounding host tissue. The conditions required for this to occur have so far not been clarified. According to *Morris* (1972) dentine and cementum encourage bone deposition on themselves only in environments that would easily form bone without them. Such an environment is considered by *Levander* (1964) to be provied by »nonspecific blastemal tissue» that according to him is formed whenever tissue is damaged and in close association with capillary formation. Bone formation in the brain tissue without the insertation of a transplant has not been experimentally demonstrated but the intrusion of the transplantation instrument naturally causes damage that presumably is followed by a local increase in capillaries that also normally are more abundant in the brain than in the subpannicular tissue. A relevant finding in this context is perhaps that of *Anderson & Parker* (1966) according to whom open or incomplete capillaries are observed in connection with endochondral ossification. Since the capillaries and their cellular elements are of mesenchymal origin it is conceivable that the osteoblasts could have differentiated from these structures (*Trueta*, 1963).

Lemoine et al. (1970) observed no lymphocytes around rat molar autotransplants whereas such cells were detected by them around molar homotransplants. The occurrence of lymphocytes in the vicinity of the present transplants even after longer postoperative periods may also be related to the immunological status of the transplants; however, it is tempting in this connection to consider *Maximow's* (1932) concept that the lymphocytes are multipotential cells, perhaps here even capable of osteogenic activity.

According to *Simpson* (1964) the ependyma and/or its associated glia cells are responsible for cartilage differentiation in lizard tail regeneration. The significance of ependymal cells with regard to ossification has been touched upon earlier in connection with intracerebral transplantation of cartilage (*Rönning*, 1966; *Rönning & Koski*, 1969); this is not clarified any further in the light of the present results. However, under certain circumstances the ependymal cells appear to be closely associated with mineralization inasmuch as the choroid plexus, that is covered by ependymal cells, may occasionally develop calcium containing hyaline formations that have been termed concentric bodies (*Findlay*, 1899). Such concentric bodies of the brain are probably

degenerative changes but the mechanism of their formation is not known (*Hudson*, 1960). In the present experiment similar structures were seen at 540 days inside the capsule of two transplants. The concentric formations seemed to occupy locations that on earlier observation days were cyst-like structures congested with decomposed erythrocytes. The fact than the concentric formations were not more common in the brain tissue of the present animals would indicate that the transplant dentine could less probably be held responsible for their development. In the dental pulp somewhat similar structures, the so-called false denticles, are considered to represent regressive changes (*Orban*, 1957).

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