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Reconstruction of the Mandible by Means of a Similar Allogenic Lyophilized Mandibular Segment*

I. Morphological and immunological studies in monkeys

Hermann F. Sailer

Clinic of Maxillo-Facial Surgery (Director: Prof. H. L. Obwegeser, M.D., D.M.D.), University Hospital Zurich, Switzerland

tongue resection to prevent postoperative relapse. In case 1 we performed tongue resection because the patient showed not only macroglossia but also many of the signs mentioned above. There are many methods for tongue resection, but we selected the Obwegeser method in this case, because this method can reduce both length and width of the tongue.

Conclusion

The *Obwegeser* II (1964) method is specially indicated for severe mandibular prognathism with open bite. The operation procedure is difficult, but good results can be obtained without complications. In order to prevent relapse tongue resection is necessary when macroglossia accompanies these cases.

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I. Morphological and immunological studies in monkeys

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Summary

Subperiosteal resection of the entire ramus including the condyle followed by immediate reconstruction using a similar allogenic lyophilized mandibular segment was performed in 5 adult monkeys (Macaca irus). One further animal served as a control for the operative technique and another provided the initial 2 rami for implantation into the first of the 5 experimental animals, while an additional animal was used to supply fresh bone specimens for immunological studies. Sequential polychrome labelling with oxytetracycline, DCAF and haematoporphyrin was used, and X-rays were taken at regular intervals; the reconstructed condyles proved to be radiographically and macroscopically indistinguishable from those of the control side. All reconstructed bone transplants took. Immunological investigations (leukocyte-migration-inhibition tests) revealed that lyophilized allogenic bone grafts exhibit reduced antigenicity.

Key-Words: Mandibular reconstruction; Condylar reconstruction; Allogenic transplants; Freeze drying; Polychrome sequential labelling; Immunology.

Introduction

The first lyophilized hard tissue to be employed clinically was bone, as prepared by *Flosdorf* and *Hyatt* (1952). Bone similarly prepared was used with good results predominantly in orthopaedic surgery as a space retainer (*Kreuz* et al. 1951, 1952, *Carr* and *Hyatt* 1955, *Gresham* 1964a, b, *Brown* and *Towsend* 1970) or as a filling material in treating cystic defects in bones of the extremities (*Wilber* and *Hyatt* 1960, *Mlynek* 1969, *Spence* et al. 1969) or within the jaws (*Marble* 1968). The utilization of lyophilized bone in orthopaedic surgery of the jaw and face region was reported by *Epker* et al. (1976). *Mellonig* et al. (1976) and *Sepe* et al. (1978) introduced lyophilized bone to the practise of periodontal surgery. In animal experimental investigations lyophilized bone was virtually unanimously estimated as being favourable for transplantation (*Cooksey* 1954, *Turner* et al. 1955, *Gresham* and *Thomas* 1962, *Heiple* et al. 1963, *Lane* et al. 1972). In all named publications lyophilized bone (we propose the name Lyo-Bone) was employed as a filling material or space maintainer. Of revolutionary significance for reconstructive surgery in the jaw and facial skeleton region was the successful transplantation of complete allogenic lyophilized mandibular segments taken from recent cadavers (*Plotnikow* 1966). Thirty-eight primary and eleven secondary mandibular reconstructions were carried out in this manner.

The advantages are thus not only the elimination of two operative procedures to be experienced by the patient, but also the ideal shape and form of the transplant obtainable.

In addition *Plotnikov* (1966) employed the simultaneous use of autogenous bone marrow in combination with lyophilized allogenic mandibular segments. *Burwell* (1963) demonstrated by means of animal research that the prior removal of bone marrow from a transplant induced a reduced host reaction to the transplant. Modelling their work on *Burwell*'s (1963) investigations, *De Fries* et al. (1971) transplanted lyophilized allogenic mandibular segments which acted additionally as receptacles for the patient's own bone marrow, thereby obtaining the advantage of an ideal form of transplant; however with the added disadvant-

* Dedicated to Prof. *H. L. Obwegeser* on his 60th birthday

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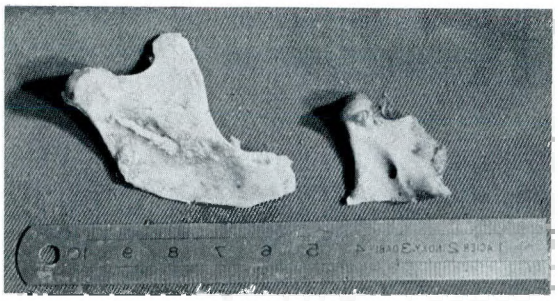


Fig. 1 Lyophilized mandibular transplant on the left, requiring reduction to the size of the resected segment on the right, from which the coronoid process has been retained in order to attach the transplant to it by means of a screw.

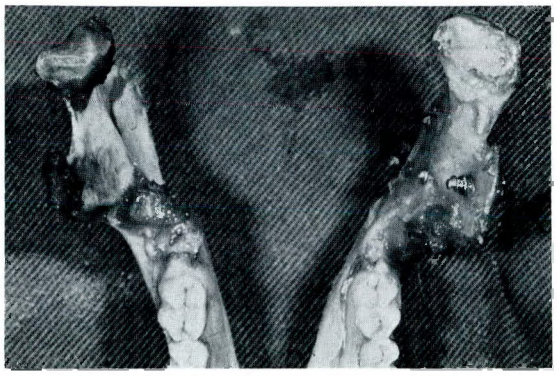


Fig. 2 Symmetrical mandibular structures 6 months postoperatively. Screw points are visible on the lingual side of the ramus.

age of subjecting the patient to a second operative procedure. The results of this work are by no means convincing and are inconsistent with *Plotnikov*'s (1966) investigations. As it was not possible to clarify the situation with *Plotnikov* (1966) further, we performed subperiosteal resections of the mandibular rami in adult monkeys, followed by immediate reconstruction using a lyophilized allogenic transplant, of a similar segment of mandible. A crucial point of the investigation was to establish the behaviour of the condyle. The study was conducted in the research establishment of the Royal College of Surgeons of England.

Materials and Methods

Eight adult Macaca irus monkeys were used experimentally, owing to the exceptional similarity between the form of their mandibles and joint function with that of humans. Extrapolation of results to the human situation is thus possibly appropriate.

As resection and immediate reconstruction had as yet not been attempted in Macaca irus monkeys, the behaviour of the animals in response to such an intervention was open to speculation. Furthermore, we wished to test the stability of a strong fixation appliance (Vitallium Finger-plates, Howemedica), consequently the ramus and condyle at the level of the angle of the mandible was resected from an extraoral approach in an animal, and immediately replaced in the same animal and fixed

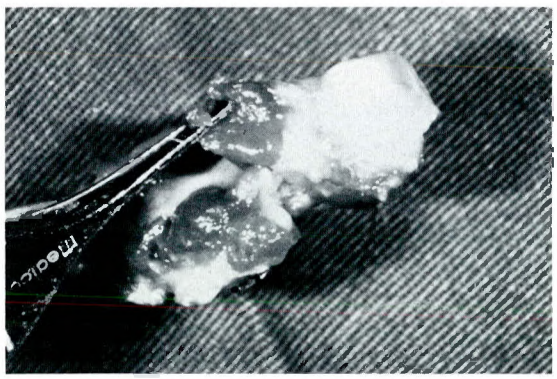


Fig. 3 Forceps hold the re-inserted lateral pterygoid muscle. The joint surface is intact 6 months postoperatively. (From H. F. Sailer: Dtsch. zahnärztl. Z. 35 (1980) 11

by means of 2 fingerplates. A slight compression was attained by application of eccentrically located screw holes in the bone. Intermaxillary fixation was not applied. A three gram piece of fresh allogenic bone was taken from another experimental animal and transplanted to the submandibular region on the opposite side in this animal, allowing the host reaction to the antigenic challenge of fresh allogenic bone to serve as a positive control in the immunological investigations.

The availability of bone for transplantation was met by sacrificing one animal initially and removing both rami including condyles. The prepara-

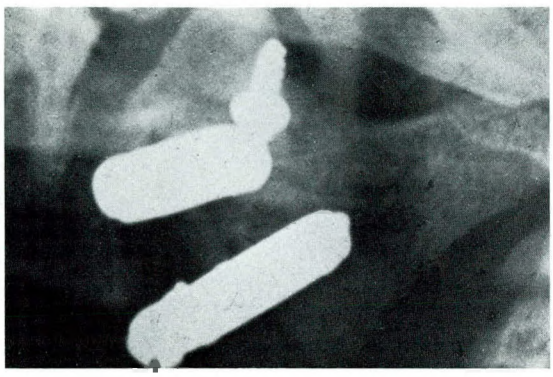


Fig. 4a

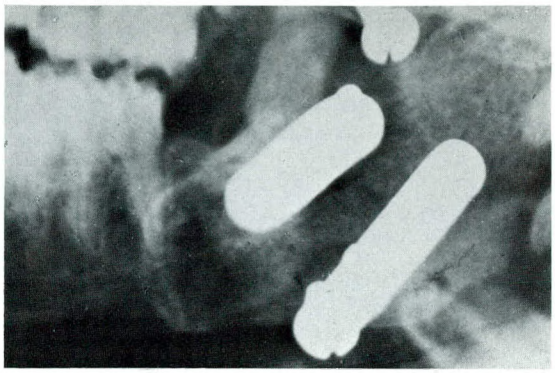


Fig. 4b

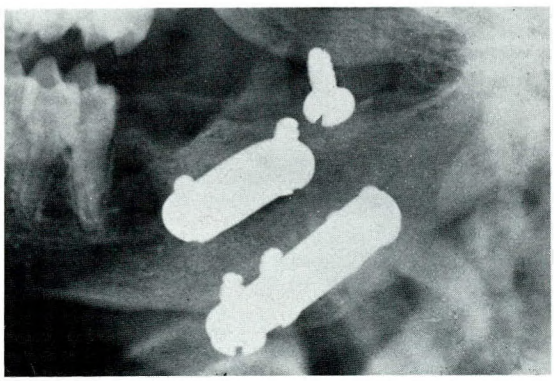


Fig. 4c

Fig. 4a–c Radiological progress: 1 week postoperatively a) the osteosynthesis site is clearly visible, after 4½ months b) unification in this region is as yet not totally completed; minimal resorption is evident in the mandibular angle region. After 6 months c) a true osteotomy junction is no longer recognisable; the initial form of the transplant is virtually completely maintained.

tions were then immersed in sterile solutions compounded to conform with that as proposed by *Zurbuchen* et al. (1959) for cartilage: NaCl 4.5, $NaHCO_3$ 8.4, Phenol red 0.005, Aqua dist. ad 500.0. From this solution (pH 6.8–8.0) a 1% solution of Beta-propiolactone was made, into which the bone segments were immersed for 2 hours.

The sterile bone segments were then rinsed twice in a sterile buffer solution for two hours at a time.

95 ml of: 1.81 gm of KH_2PO_4 diluted with 200 ml Aqua dist.
405 ml of: 5.93 gm of Na_2HPO_4 (Sørensen) diluted with 500 ml Aqua dist.

500 ml

In this manner the toxic and carcinogenic Beta-propiolactone was washed from the bone. Thereafter the sterile bone was transferred to the freeze-drier, in which it was deep frozen at –60 °C for one hour, and then dried for 7 days. Storage was under vacuum in an air-tight metal container.

Prior to usage the bone preparation was rehydrated for 12 hours in an antibiotic solution (Penicillin 10 Mio./1) and then, as described above, implanted initially into 2 experimental animals by means of an extraoral approach. The rami thus resected from these animals were sterilised in Beta-Propiolactone, lyophilized, rehydrated and transplanted into the next animal, being fixed by means of screws to the retained coronoid processes in the first two cases, and by means of interosseous wiring in the following cases. Altogether 5 Macaca irus monkeys underwent unilateral subperiosteal resections and simultaneous reconstruction with

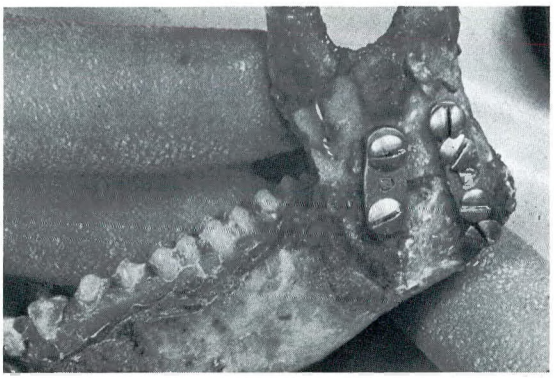


Fig. 5a



Fig. 5b

Fig. 5a–b Macroscopic findings: after 39 days a) no indication of replacement of the transplant is evident (soft tissues are still attached to the upper part of the ramus), while after 4'/2 months b) it is predominantly completed.

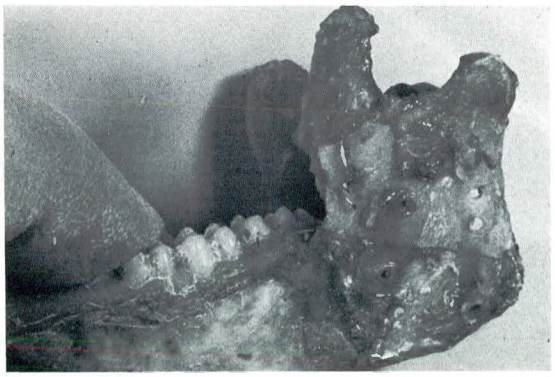


Fig. 6 After removal of the plates, the unification between the transplant and the mandible is firm, such that disruption was not manually possible.

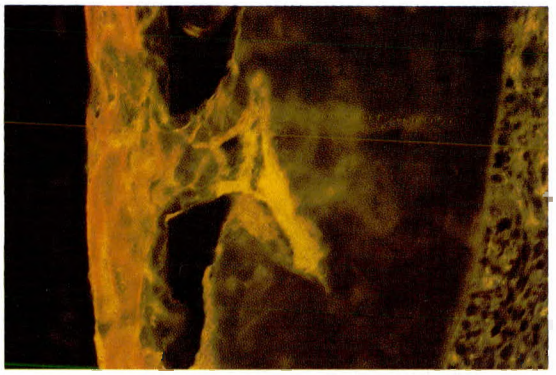


Fig. 7 Optical fluorescent findings after 39 days: In the Osteosynthesis region and the entire medulla (right side) deposition of fluorescent substances is evident; Haversion canals penetrate the cortex (middle); deposition of calcified tissues is taking place subperiosteally (left). (X 50)

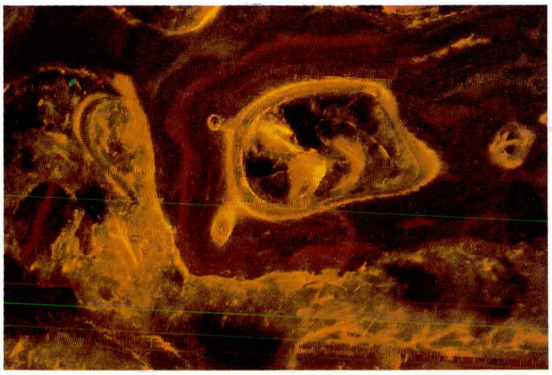


Fig. 8 4'/2 months postoperatively lamellar bone regeneration in the osteosynthesis area can be seen (× 100).

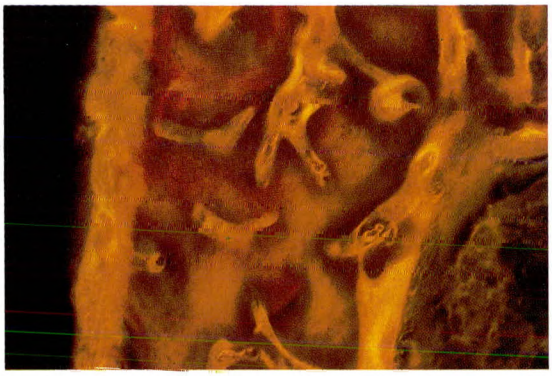


Fig. 9 With the aid of fluorescent substances, it is possible to recognise a near complete replacement of cortex after 6 months (X 50).



Fig. 10 Re-opened joint capsule with a view of the lower joint space. (From H. F. Sailer: Dtsch. Zahnärztl. Z., 35 (1980) 11).

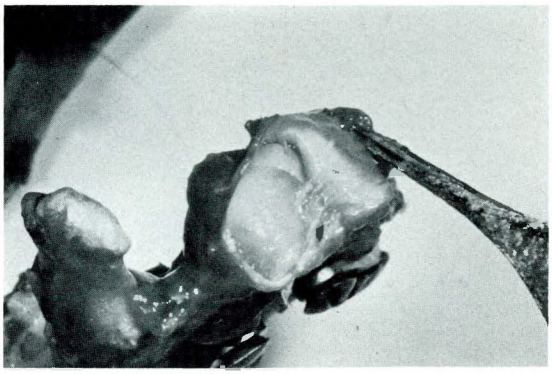


Fig. 11 Minimal disc adhesions after 4½ months observation, completely smooth joint surfaces remain on the transplant.



Fig. 12 The joint surface is covered by a delicate connective tissue layer, which is lifted here by the point of a scissor.

these allogenic mandibular segments. Each animal received 1 ampule of Triplopen i.m. daily for 3 days postoperatively, and had control X-rays taken weekly. Moreover, polychrome sequential bone marking (*Olerud* and *Lorenzi* 1970) using oxytetracycline (150 mg./kg.) with the total dosage being administered over a period of 2 consecutive days, 2 weeks postoperatively, and DCAF (Di (Corboxymethyl)-Aminomethyl) Fluorescein), 4 weeks postoperatively (Dose 25 mg./kg.) and Haematoporphyrin (Dose 300 mg./kg.) 2 months postoperatively was undertaken on each animal.

To determine the antigenicity of fresh allogenic and lyophilized allogenic transplants the leukocyte-migration-inhibition test (*Søborg* and *Bendixen* 1967) was employed. The diminished propensity for Macaca irus white blood cells to sediment in comparison to human white blood cells led us to attempt obtaining sufficient leukocytes (more than 10^7/ml.) by layering 10 ml. of venous blood on to a mixture of 9% Ficoll and Triosil 350 (1 : 4) and centrifuging it for 5 minutes at 400 revolutions/min., and repeating this 5–8 times, pipetting off each time the supernatant leukocytes thus gained. The production of the necessary antigens for the conduction of the leukocyte-migration-inhibition test was achieved as follows: Freeze-dried cortiomedullary blocks were finely filed under sterile conditions and homogenised in culture medium (Medium 199, Flow-laboratories) and then pressed through a Millipore-Filter (pore size 0.22 micron) and finally diluted by means of Medium 199 into various antigen concentration preparations.

The animals were sacrificed after 39 days, 2, 3, 4½ and 6 months by intracardiac injection of Vetalar.

Results

Owing to the lack of intermaxillary fixation the animals stressed the transplants immediately postoperatively and ate their normal diet (cakes, eggs, bananas) thus avoiding the necessity for tube feeding. Sutures were removed eight days postoperatively. Neither early nor late infection occured in either the control or any of the five animals who

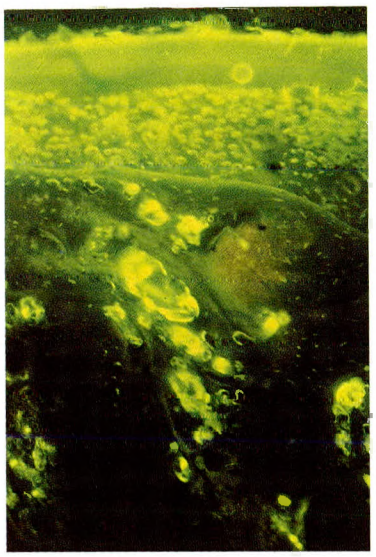


Fig. 13a

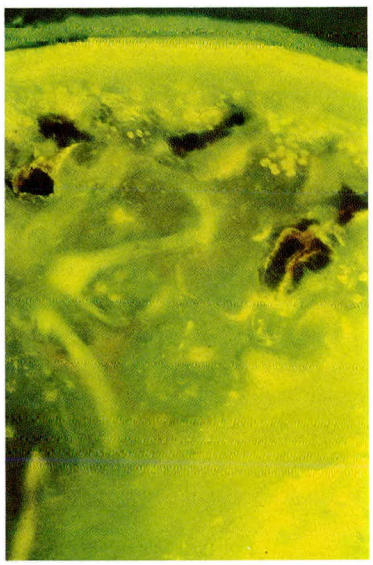


Fig. 13b

Fig. 13a–b Undecalcified bone section of the condyle: The joint surfaces were intact during the entire period of observation. Bone replacement – still in progress after 39 days a) – is largely completed after 6 months b); some indication of resorption is seen in the cartilaginous zone (X 50).

received lyophilized mandibular transplants. The transplants accurately matched the resected jaw segments, thus maintaining symmetrical contour (Fig. 1, 2). Whilst a deviation of the mandible to the operated side occurred during the first few weeks after the operation, this was soon alleviated as was evident during aggressive conduct with jaw opening and baring of teeth, or yawning. The basis for this improved functional capability was to be found in the preparations where the M. pterygoideus lateralis was seen to re-insert into its normal anatomical position (Fig. 3). Radiologically, retarded bone regeneration was evident during the first 2 months, and only after $4^1/_2$ months was the osteosynthesis barely recognizable (Fig. 4a, b, c). Radiological and macroscopical findings coincided; though the transplant as such was fully recognizable after 39 days (Fig. 5a), this was not the case after $4^1/_2$ months (Fig. 5b).

Nevertheless at 39 days a strong union between transplant and mandible already existed, which we regard to be functionally stable even without plates (Fig. 6). Undecalcified bone sections indicate (Fig. 7) that at this stage the medullary spaces reveal excellent regenerative processes as indicated by the incorporation of fluorescent materials; subperiosteal new-bone formation with Haversian canals within the cortex is also visible (Fig. 7).

After $4^1/_2$ and 6 months only minimal portions of the allogenic transplant were macroscopically evident (Fig. 5, 6). Undecalcified bone sections after $4^1/_2$ months show excellent bone replacement (Fig. 8). After 6 months the graft appeared to be totally replaced; utilizing the polychrome sequence marking technique it was possible to demonstrate that the compact bone was now also replaced (Fig. 9).

The most astonishing findings were those relating to the joints, as the joint on the transplanted side functioned in a manner equal to that of the non-operated side. The joint capsule was both intact and unscarred. A normal upper and lower joint space was evident (Fig. 10). The articular disc, not operatively interfered with, demonstrated very few adhesions in one case after $4^1/_2$ months (Fig. 11).

As mentioned above the reinsertion of the previ-

ously detached M. pterygoideus lateralis onto the transplant had occurred (Fig. 3). The condyle was covered by a delicate connective tissue layer (Fig. 12). Thus, after both 39 days and 6 months the joint surfaces of the transplant are seen to be largely intact. Throughout the entire period of observation, the joint surface remained preserved (Figs. 2, 3, 11, 12, 13 a, b). The bone regeneration in the condylar region had predominantly ceased after 6 months, however minimal areas of resorption were visible in the cartilaginous zone (Fig. 13 b).

The leukocyte-migration-inhibition test demonstrated that lyophilized allogenic mandible exhibits a residual antigenicity, though clearly of a lesser magnitude than allogenic fresh bone, which is accordingly resorbed within $2^1/_2$ months. The number of experimental animals used in this study is too small to allow exact assertions concerning residual antigenicity to be made, nevertheless it was evident that a 500 to 1000 times greater dose of antigen containing lyophilized material was needed than in the case of fresh allogenic bone in order to achieve a leukocyte migration inhibition of the same degree.

Discussion

We wish to indicate that experimental results achieved on non-human primates are only transferable to humans with certain limitations. The following considerations must thus be regarded with this viewpoint in mind, in addition to the fact that our investigations only extended over a 6 month period.

Our animal experimental studies on monkeys support the clinical results reported by *Plotnikov* (1966). The osseous form of a lyophilized mandibular segment cannot be achieved by means of an autogenous rib or iliac crest transplant. On the basis of our experimental findings lyophilized mandibular segments should provide good functional results. The good results may possibly be due partially to the fact that the resection and reconstruction was carried out subperiosteally thus allowing for effective periosteal new bone formation. Nevertheless, simultaneous new bone formation was also shown to occur in the end-to-end osteosynthesis medullary areas by fluorescent microscopic studies.

Kazanjian (1946), *Francksen* (1958), *Haunfelder* (1962) and *Steinhardt* (1967) reported on spontaneous mandibular regeneration following subperiosteal resection without concomitant reconstruction. Most of their cases were children and juveniles in whom very active bone regeneration occurs. Compared with this, all our experimental animals were adults. Spontaneously regenerated mandibular segments are not as cosmetically acceptable compared with the results obtained when using similar lyophilized mandibular segments.

Owing to the highly sensitive nature of the Macaca irus, intermaxillary fixation was not applied, thus allowing immediate postoperative functional stressing of the lyophilized transplant. Whether this early stressing of the transplant had a favourable effect on it, as would appear to be the case with autogenous bone transplants (*Steinhäuser* 1968) we are, without comparable experimental studies, not able to arrive at a definitive answer. On the contrary though, our investigations revealed with certainty that allogenic, lyophilized bone transplants are replaced more slowly than autogenous bone. This confirms the work of *Kreuz* et al. (1951) and *Gresham* and *Thomas* (1962).

Our immunological investigations, whereby lyophilized bone exhibited a diminished antigenicity, agree with the results achieved by other researchers (*Kreuz* et al. 1951, *Chalmers* 1959, *Brooks* et al. 1963, *Kossowska-Paul* 1966, *Burwell* 1976, *Friedländer* 1976). The residual antigenicity appears to be so weak that rejection or resorption does not occur. However, on the basis of our investigations, an enhancement can not be excluded. A residual antigenicity is perhaps a requisite to encourage an insidious substitution of the allogenic bone transplant such that true incorporation can occur. On the grounds of the complication-free incorporation of all the allogenic, lyophilized mandibular segments in our investigations, we conclude that the prior removal of the medulla as suggested by *De Fries* et al. (1971), is not necessary when employing disinfection, lyophilization and subperiosteal resection and reconstruction techniques in the manner outlined herein.

Conclusion

On the basis of our experimental investigations we conclude:

1. Macara irus monkeys prove to be excellent research animals for mandibular resection and immediate reconstruction without intermaxillary fixation.
2. Lyophilized allogenic mandibular segments are outstanding experimental reconstruction material.
3. Removal of the bone marrow under the given experimental conditions in order to reduce antigenic potential, is not deemed necessary.
4. The retarded transplant replacement process, in contrast to autogenous transplants, proved to have no functional disadvantages.
5. A certain residual antigenicity for the resorption and regeneration i.e. for the complete incorporation, of allogenic, lyophilized osseous material, is possibly necessary.

Acknowledgement

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