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Tissue-separating capacity of growth cartilages

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SUMMARY The tissue-separating capacity of chondral structures has been debated for more than 30 years, and one aspect that has particularly been questioned is whether the secondary cartilage of the mandibular condyle is comparable to primary growth cartilage, e.g. the epiphyseal growth plate.

The present report summarizes information gained by using a specific interosseal transplantation method. These findings lead to the conclusion that all the structures examined, i.e. the proximal epiphyseal cartilage of the tibia, the cartilage of the costochondral junction of the ribs, the basicranial synchondroses, the medial cartilage of the clavicle and the mandibular condyle, have the capacity to separate adjoining skeletal structures.

The changes induced by the transplanted structures in the recipient area vary, however, suggesting a hierarchial arrangement of cartilages with regard to their tissue-separating capacity. It is suggested that the tissue-separating capacity is a basic phenomenon in the function of growth, not only of primary growth cartilages, but of secondary cartilages as well.

Introduction

Certain constituents of organisms, e.g. adipose and muscular tissues, may upon increasing displace the surrounding structures, i.e. they have a tissue-separating capacity. Opinions differ on the separating forces involved in the growth of the structurally more rigid and morphologically diverse skeletal components, and consequently these have been subjected to detailed analysis. In the craniofacial area, the growth of the brain in particular is considered to exert a force on the overlying bones causing them to move apart, which is adjusted for by apposition on the edges of the suture (Young, 1959). In addition, the growth of the eyeballs and cartilaginous structures (Scott, 1954, 1962), and also of the oral, nasal and pharyngeal cavities, is regarded as being of paramount importance (Moss, 1962).

Clinical and experimental findings have indicated that chondral structures, such as epiphyseal growth plates, may possess a tissue-separating force (Blount and Clarke, 1949; Strobino *et al.*, 1952). According to Baume (1961), a 'place of endochondral ossification with tissue separating force' is to be termed a *growth centre*, although Koski (l985) maintains that the use of the term ought to be discontinued in view of the lack of acceptable evidence for the existence of such cartilaginous sites in the craniofacial skeleton. Thus, the crucial question is whether chondral structures located between the bones of the head are able to force the bones apart, i.e. do they possess a tissue-separating capacity. Another important aspect of the discussion has been whether the cartilage of the mandibular condyle, a secondary cartilage, is comparable to the epiphyseal cartilage of a long bone, a primary cartilage, in its tissue-separating capacity. The problem has been approached using a number of tissue transplantation methods.

The experiments have indicated that primary cartilage transplants in a 'non-functional' environment, most often subcutaneous or in the brain tissue, increase in length and retain their typical microstructure for extended periods (Barnicot, 1941; Lacroix, 1951; Gilette *et al.*, 1956; Schatten *et al.*, 1958; Felts, 1961; Holtrop, 1964; Harris *et al.*, 1965; Duterloo, 1967; Koski and Rönning, 1970; Meikle, 1975), an observation which differs from comparable ones on transplantation of the mandibular condyle (Koski and Mason, 1964; Koski and Rönning, 1965; Meikle, 1973). There are some findings,

however, to indicate that condylar transplants also survive and grow at a non-functional transplantation site, and even resemble in that respect a long bone (Rönning, 1966; Duterloo, 1967), especially if the experimental design allows the maintenance of a function/biomechanical stimulus on the condylar transplants (Peskin and Laskin, 1965; Ware and Taylor, 1965; Duterloo and Wolters, 1971; Engelsma *et al.*, 1980; Kantomaa and Hall, 1988a,b; Rönning and Peltomäki, 1991).

Despite these findings, the tissue-separating nature of cartilages has been inadequately assessed, mainly due to methodological shortcomings. Copray *et al.* (1985) developed an *in vitro* method which facilitated examination of the growth pressures produced by various cartilages. All the cartilages examined, from metatarsals, ribs, skull base and the mandibular condyles, appeared to generate growth pressure, but that of the condyles and synchondroses was less marked than the other two (Copray *et al.*, 1986). A recipient site where the transplants grow under external pressure *in vivo* would appear to be especially suitable for examining the tissue-separating force of cartilaginous structures. A transplantation design meeting these requirements was introduced by Kylämarkula and Rönning (1979) and further developed by (Rönning and Kylämarkula, 1982). This report reviews the information gathered using the above method, confirming the tissue-separating properties of different cartilages.

Materials and methods

The transplantations were carried out on 10-day-old Long–Evans rats of the Turku strain. Epiphyseal cartilages of the proximal end of the tibia, cartilages of the costochondral junction, spheno-occipital synchondroses of the basicranium, medial cartilages of the clavicles and cartilages of the mandibular condyles, all with some adjoining bone, were dissected out and stored in physiological saline until transplanted. Next, the calvarium of a sex-matched litter-mate, or, in the case of rib transplants, the calvarium of the same animal, was exposed and an opening corresponding to the transplant outline was cut across the interparietal suture. The transplant was then gently inserted to replace the extirpated bone fragment. The cartilage portion of the rib sections varied, being either short, intermediate or long. Tibia transplants required some size-reducing trimming before transplantation. In addition, pieces of calvarium joined by the interparietal suture were interchanged between rats to serve as sham controls alongside unoperated control rats (Figure 1). At completion of the transplantation, the skin wound was closed with collodion.

The animals were killed at 35 days, i.e. 25 days after the operation, and the skulls were freed from soft tissues for craniometry. A sliding caliper was used to measure two dimensions on the dry skulls: calvarial width, the distance between the temporal crests, and neurocranial width, the intertemporal distance immediately superior to the zygomatic process (Figure 2). The mean value of each group was compared with the control group by means of Student's *t*-test. Since our special interest was the behaviour of secondary cartilages (clavicular and condylar cartilages), the mean values of the animals with these transplants were also compared with the other groups. Tissue samples from the transplant area of each group were prepared for histological examination.

The reliability of the measurements was tested by measuring 20 skulls twice and calculating the measurement error for each variable from the formula $\sqrt{(d^2/2n)}$, where d is the difference between the first and second measurements.

Results

Transplantation of most of the cartilages across the interparietal suture was followed by a widening of the neurocranium as compared with the unoperated rats (Table 1). The widening was not equal among the groups, however. Transplantation of the epiphyseal cartilage of the proximal end of the tibia and the costochondral junction with a long cartilaginous end led to a widening exceeding that caused by the other transplants. The statistics indicated that the skulls with the tibia transplant showed only a tendency ($P < 0.05$) to being wider than that of

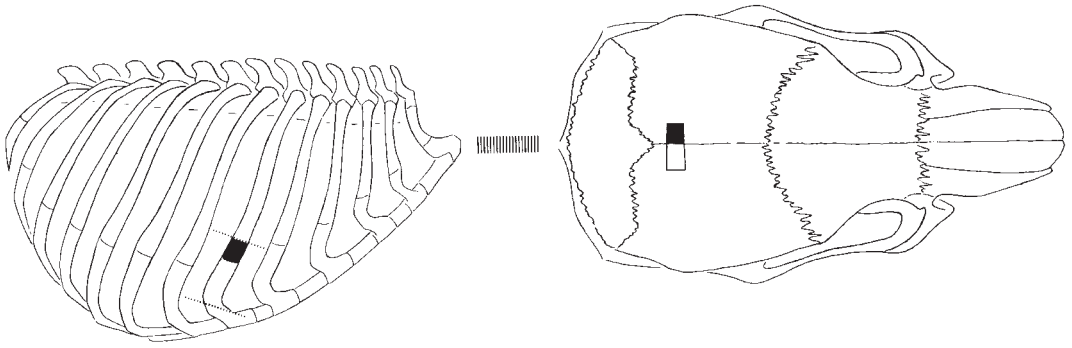

Figure 1 The experimental design. Various cartilage-containing sections were transplanted across the interparietal suture to a site prepared by removing pieces of the parietal bone corresponding to the outline of the transplant. As an example, transplantation of costochondral sections with various lengths of cartilage is illustrated.

the secondary cartilage groups. This was probably related to a minor methodological detail, i.e. unlike other transplants the tibia required some size-reducing trimming which inevitably led to a larger variation in this group than in the others. Interestingly, the width of the neurocranium was comparable between the rats with the cartilage of the medial end of the clavicle and the mandibular condyle, the width being slightly greater than in the unoperated control rats, but significantly smaller than in rats with the costochondral transplants (intermediate and long cartilage portion). The interchange of bone traversed by a suture, and the costal cartilage transplants with a short cartilaginous end did not seem to have any notable effect on the neurocranial morphology as compared with the unoperated rats.

Measurement errors, 0.10 and 0.01 mm for the calvarial and neurocranial widths, respectively, were regarded as insignificant as far as the reliability of the results is concerned.

Histological examination revealed that most of the transplants had retained a normal endochondral ossification apparatus, although the amount of cartilage was frequently less than in the corresponding structure *in situ*. The transplants with epiphyseal cartilage of the tibia and costal cartilage with long and intermediate portions seemed to undergo the least structural deterioration. A tendency for bridging over the synchondroseal cartilage with bone was noted in some of the transplanted spheno-occipital

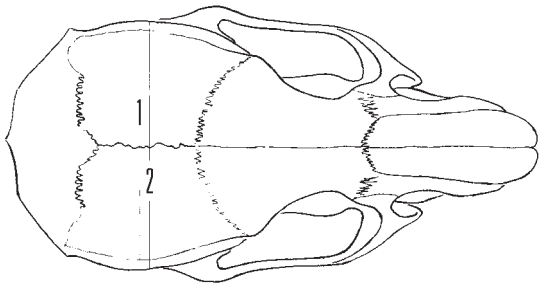

Figure 2 Measurements made on dry skulls. Calvarial width (1), distance between temporal crests, and neurocranial width (2), intertemporal distance immediately superior to the zygomatic process.

synchondroses, and the replacement of cartilage by bone was even more evident in the costal cartilage transplants with a short cartilaginous end, i.e. virtually no cartilage was left at the end of the observation period. The condylar cartilage transplants showed a reduced number of hypertrophic cells in particular, and less affinity for alcian blue, indicative of reduced synthesis of cartilage matrix components.

Discussion

Among a variety of possible experimental approaches, this interosseal transplantation method is designed especially to address the question of the tissue-separating capacity of cartilage-containing structures *in vivo*. The

Table 1 Transverse measurements (in mm) of the neurocranium in rats on which various cartilage-containing sections were transplanted across the sagittal suture at 10 days of age and measured at 35 days.

	Calvarial width		Neurocranial width		
	X	SD	*X*	SD	*n*
Costal cartilage 3	>14.4***	0.41	>16.0***	0.25	15
Proximal end of tibia	14.0*	1.12	>16.1*	0.70	10
Costal cartilage 2	>13.9***	0.60	>15.7***	0.26	15
Spheno-occipital synchondroses	13.5***	0.33	>16.0***	0.30	10
Medial end of clavicle	**13.4***	**0.23**	**15.5****	**0.24**	15
Mandibular condyle	**13.4***	**0.19**	**15.4***	**0.21**	15
Suture (= sham)	13.0	0.26	15.4	0.29	10
Costal cartilage 1	>12.9	0.21	>15.2	0.18	15
Control	13.1	0.18	15.2	0.21	45

Costal cartilages 1, 2 and 3 refer to a short, intermediate or long cartilaginous end in the transplant, respectively. The probability of the difference between experimental and control rats is calculated by means of Student's *t*-test: *$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$.
Arrowheads indicate that the groups are significantly different from those with secondary cartilage transplants (bold figures; $P \leq 0.05$).

capacity could be determined by inference from the cumulative growth of the recipient area, the neurocranium. It could naturally be argued that the operation *per se* may have a transient role in the increased widening of the neurocranium (Peltomäki, 1993), but the mechanical force can evidently have lasted only for a limited period, just a few days, since the neurocranium was at a stage of rapid growth (Baer, 1954). Furthermore, depending on the recipient site, the transplanted structures may not have any effect on the neurocranial morphology, any more than sham procedures (Kylämarkula and Rönning, 1979; Rönning and Kylämarkula, 1982). Thus, it is plausible that the widening of the neurocranium was due to the growth of the transplants, which not only kept pace with normal growth, but exceeded it in order to cause the expansion. One may also ask whether difference in experimental design, i.e. use of autogenous versus isogenous transplants, could affect the results. It has been noted, however, that transplantation has a comparable effect on the neurocranium irrespective of this difference in tissue compatibility (Kylämarkula and Rönning, 1983; Peltomäki and Rönning, 1991, 1993).

The present findings support the view that (with some exceptions) all the structures examined have as transplants an ability to push skeletal elements apart, i.e. they possess a tissue-separating capacity. This conclusion agrees well with that of the *in vitro* experiment of Copray *et al.* (1986) who calculated the amount of growth pressure from the deflection of the arm-traps between which the cartilages were inserted.

Upon termination of the experiment, only the costochondral transplant with a short cartilaginous end seemed to have adapted to the transplantation site, as deduced from the finding that no difference was noted between the unoperated skulls and the ones with the above transplant.

The mandibular condyle and the medial end of the clavicle, composed of secondary cartilage and regarded as adaptive structures (Scott, 1954; Moss, 1962; Koski, 1968; Carlson *et al.*, 1980; Stutzmann *et al.*, 1991; Henning *et al.*, 1992), generated an expansive force which, however, reportedly diminishes with time (Rönning and Peltomäki, 1991; Rönning *et al.*, 1991). It is plausible that with longer observation periods, the forces at the recipient site that resist separation of the bones may increase and eventually outweigh the tissue-separating capability of any cartilage. It should also be

noted that a 'non-functional' transplant may not favour the continuation of clavicular and condylar cartilage differentiation, for which a biomechanical stimulus is regarded as being necessary (Hall, 1986; Rönning and Kantomaa, 1988; Tran and Hall, 1989; Stutzmann *et al.*, 1991). Mobile function cannot be entirely excluded as a factor affecting the transplants, however, as the recipient site between the parietal bones shows some mobility (Kylämarkula and Rönning, 1979), which has been found in dogs to be related to age and arterial blood flow (Oudhof and van Doorenmaalen, 1983). Articulatory function cannot be viewed as a prerequisite for the force generated by the condylar cartilage, however, although it is evidently a modifying factor (Meikle, 1973; Copray *et al.*, 1985; Rönning and Peltomäki, 1991), and of significance for the maintenance of the cartilage (Rönning, 1966). The nasal cartilage, suggested by Scott (1954, 1962) to have an important morphogenetic role, is even less under the influence of a mobile function and yet resumes its morphogenetic role after a provoked temporary disturbance (Rönning, 1971; Dixon and Styrt, 1994).

The findings suggest, again in line with Copray *et al.* (1986), that epiphyseal cartilages have more tissue-separating capacity than clavicular or condylar cartilages, for example, but certain reservations must be made regarding this straightforward interpretation. The magnitude of the force generated by a cartilaginous structure may not be as crucial for the growth of the skeleton as only a minor load exceeding the resistance of the structures is involved. The relative effect of any cartilage, i.e. the magnitude of the force it generates, probably varies with age even during the active growth period. For example, the reduction in the amount of condylar cartilage can be regarded as reflecting the gradual shift of its role from mainly a growth cartilage to a less adaptive articular one (Carlson *et al.*, 1980; Vinkka 1982; Copray *et al.*, 1988; Vinkka-Puhakka, 1991). The present results, therefore, provide an insight into the tissue-separating capacity of the cartilages at the given time interval without being able to address their total potency covering the entire growth period; neither do they allow us to conclude that these cartilages necessarily possess the same tissue-separating capacity at their original site as at the non-functional site used. One would rather suppose that local conditions modify the tissue-separating quality, since the growth of cartilages is considered to be influenced, at least partly, by site-specific organs and functions (Moss, 1981). Consider, for example, the difference in mobile function between the costal cartilage of the ribs due to breathing and the condylar cartilage of the mandible due to oral functions.

The various growth cartilages are specific micro-architectural and biochemical variations of the same basic structure. What, then, is the reason for the evident difference in tissue-separating capacity between primary and secondary cartilages? According to Koski (1981), the difference in dividing cell populations is the essential separating characteristic and provides a clue to the behaviour of the cartilages. Undifferentiated prechondroblasts constitute the mitotic cells of secondary cartilage, whereas in primary cartilage most of the dividing cell population consists of true chondroblasts (Blackwood, 1966; Folke and Stallard, 1967; Öberg *et al.*, 1967; Joondeph, 1972; Kember, 1978; Heeley *et al.*, 1983; Petrovic, 1984; Luder *et al.*, 1988). This difference could explain the observed minor effect of growth hormone on condylar cartilage growth as compared with long bone growth, for instance (Vogl *et al.*, 1993). It may turn out, however, that too much emphasis in research into the growth processes of cartilages has been laid on the proliferative cell population, simply because this has been easy to examine (Kember and Kirkwood, 1991). Other essential elements of cartilage, namely the secretion of extracellular matrix and hypertrophy of the cells, have received less attention, although they may be considered important with regard to tissue-separating capacity. In long bone growth, the cellular volume increases 10-fold and the matrix volume 3-fold from the proliferative to the hypertrophic zone, affecting longitudinal growth considerably (Hunziker *et al.*, 1987), and a comparable increase in the cellular volume has also been found to take place in human fetal

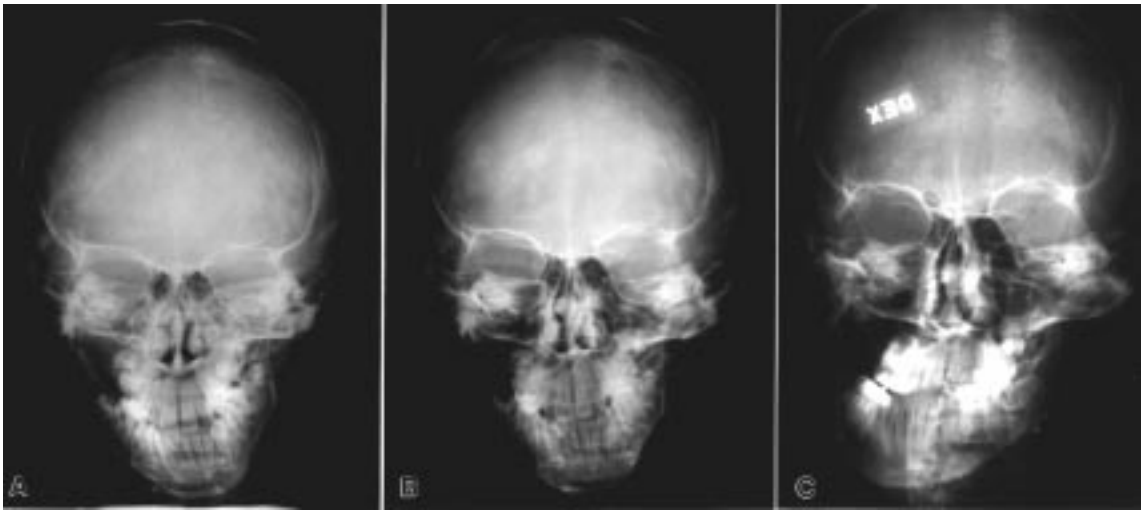

Figure 3 Progressively deteriorating asymmetry of the face associated with ankylosis of the TMJ in a 13-year-old boy (A). The condition was corrected by replacing the affected left condylar process with a costochondral graft. The chin still deviates to the left 1 year after the operation (B). Excessive growth of the mandible on the side with the graft then led to asymmetry opposed to the initial condition, 6 years post-operatively (C). (Published with the permission of the Proceedings of the Finnish Dental Society.)

condylar cartilage (Ben-Ami *et al.*, 1992) confirming the earlier postulate of the importance of chondrocyte hypertrophy for the expansion of the condylar process (Luder *et al.*, 1988; Bosshardt-Luehrs and Luder, 1991). Consequently, the considerable cell increase may also be regarded as responsible for the tissue-separating capacity of both primary and secondary cartilages.

Osmotic pressure effected by matrix proteoglycan monomers, most of which form aggregates with hyaluronan (Hardingham *et al.*, 1992), is obviously a prime factor in the generation of the tissue-separating force. A comparable osmotic force is reportedly responsible for palatal shelf elevation during the development of the secondary palate (Ferguson, 1995). The difference in the amount of proteoglycans between condylar and epiphyseal cartilage, although not yet shown directly, could be associated with a smaller osmotic pressure and tissue-separating capacity in the former.

Hall (1991) has suggested that one should look for the reason for the different behaviour of growth cartilages in earlier developmental events. Accordingly, the difference may be related to the origins of the cartilages, and the identification of skeletogenic stem cell populations would help in understanding the different growth properties of cartilages.

Growth in all cartilages must be viewed as an interplay between genetic, environmental and epigenetic factors (van Limborg, 1972; Petrovic and Stutzmann, 1981; Hall, 1991), and probably no transplantation method can differentiate between them (Koski, 1985). The findings emerging from the transplantation experiments reported here imply that cartilage-mediated growth, whether related to primary or secondary cartilage, is not only a filling-in type of growth, but that the tissue-separating capacity is an essential feature of it in general. A clinical example related to the observations presented here may allow the interpretation that in the case illustrated involving a costochondral graft, the outcome was mainly due to the tissue-separating force of the costal cartilage (Figure 3). It is evident that the magnitude of force generated by different cartilages varies, which is suggestive of a hierarchial arrangement of cartilages with regard to their tissue-separating (or adaptive) capacity, even when subjected to the same

stimuli. In other words, the tissue-separating capacity may be primarily genetically programmed.

Conclusion

The present interosseal transplantation method was designed to answer the simple question of whether growth cartilages are endowed with a tissue-separating capacity. The findings allow a clear conclusion to be reached: all the cartilages examined (the epiphyseal cartilage of the proximal end of the tibia, the cartilage of the costochondral junction of the ribs, the basicranial synchondroses, the medial cartilage of the clavicles and the cartilage of the mandibular condyles) have the ability to separate adjoining skeletal structures, i.e. they have a tissue-separating capacity. The method does not, however, support the straightforward view that the behaviour of the cartilages is necessarily the same at their original site. The growth of all cartilages, whether primary or secondary, is probabaly modulated by site-specific environmental influences, which may regulate the amount of tissue-separating force. Finally, it is suggested that tissue-separating capacity, being a combined result of gene expression and environmental influence, is an elementary feature of the growth function of both primary and secondary cartilages.

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References

Baer M J 1954 Patterns of growth of the skull as revealed by vital staining. Human Biology 26: 80–126

Barnicot N A 1941 Studies on the factors involved in bone absorption. American Journal of Anatomy 68: 497–527

Baume L J 1961 Principles of cephalofacial development revealed by experimental biology. American Journal of Orthodontics 47: 881–901

Ben-Ami Y, Lewinson D, Silbermann M 1992 Structural characterization of the mandibular condyle in human fetuses: light and electron microscopic studies. Acta Anatomica 145: 79–87

Blackwood H J J 1966 Growth of the mandibular condyle of the rat studied with tritiated thymidine. Archives of Oral Biology 11: 493–500

Blount W P, Clarke G R 1949 Control of bone growth by epiphyseal stapling. A preliminary report. Journal of Bone and Joint Surgery 31A: 464–478

Bosshardt-Luehrs C P, Luder H U 1991 Cartilage matrix production and chondrocyte enlargements as contributors to mandibular condylar growth in monkeys (*Macaca fascicularis*). American Journal of Orthodontics and Dentofacial Orthopedics 100: 362–369

Carlson D S, McNamara J A Jr, Graber L W, Hoffman D L 1980 Experimental studies of growth and adaptation of TMJ. In: Irby B (ed.) Current advances in oral surgery, Vol III. C.V. Mosby Co., St. Louis, pp. 28–77

Copray J C V M, Jansen H W B, Duterloo H S 1985 An *in-vitro* system for studying the effect of variable compressive forces on the mandibular condylar cartilage of the rat. Archives of Oral Biology 30: 305–311

Copray J C V M, Jansen H W B, Duterloo H S 1986 Growth and growth pressure of mandibular condylar and some primary cartilages of the rat *in vitro*. American Journal of Orthodontics and Dentofacial Orthopedics 90: 19–28

Copray J C V M, Dibbets J M H, Kantomaa T 1988 The role of condylar cartilage in the development of the temporomandibular joint. Angle Orthodontist 58: 369–380

Dixon A D, Styrt P J 1994 Growth changes in the craniofacial complex of the rat after prolonged papain administration. American Journal of Orthodontics and Dentofacial Orthopedics 105: 270–278

Duterloo H S 1967 *In vivo* implantation of the mandibular condyle of the rat. An experimental investigation of the growth of the lower jaw. Thesis, University of Nijmegen, The Netherlands

Duterloo H S, Wolters J M 1971 Experiments on the significance of articular functions as a stimulating chondrogenic factor for the growth of secondary cartilages of the rat mandible. Transactions of the European Orthodontic Society, pp. 103–115

Engelsma S O, Jansen H W B, Duterloo H S 1980 An *in-vivo* transplantation study of growth of the mandibular condyle in a functional position in the rat. Archives of Oral Biology 25: 305–311

Felts W J L 1961 *In vivo* implantation as a technique in skeletal biology. International Review of Cytology 12: 243–302

Ferguson M W J 1995 Development of the face and palate. Cleft Palate-Craniofacial Journal 32: 522–524

Folke L E A, Stallard R E 1967 Cellular kinetics within the mandibular joint. Acta Odontologica Scandinavica 25: 437–489

Gilette R, Mardfin D F, Schour I 1956 Osteogenesis in subcutaneous rib transplants between normal and *ia* rats. American Journal of Anatomy 99: 447–471

Hall B K 1986 The role of movement and tissue interactions in the development and growth of bone and secondary cartilage in the clavicle of the embryonic chick. Journal of Embryology and Experimental Morphology 93: 133–152

Hall B K 1991 What is bone growth? In: Dixon A D, Sarnat B G, Hoyte D A N (eds.) Fundamentals of bone growth: methodology and applications. CRC Press, Boca Raton, pp. 605–611

Hardingham T E, Fosang A J, Dudhia J 1992 Aggrecan, the chondroitin sulfate/keratan sulfate proteoglycan from cartilage. In: Kuettner K E, Schleyerbach R, Peyron J G, Hascall V C (eds.) Articular cartilage and osteoarthritis. Raven Press, New York, pp. 5–19

Harris W R, Martin R, Tile M 1965 Transplantation of epiphyseal plates. Journal of Bone and Joint Surgery 47A: 897–914

Heeley J D, Dobeck J M, Derice R A 1983 [^{3}H]thymidine uptake in cells of rat condylar cartilage. American Journal of Anatomy 167: 451–462

Henning T B, Ellis E III, Carlson D S 1992 Growth of the mandible following replacement of the mandibular condyle with the clavicle: an experimental investigation in *Macaca mulatta.* Journal of Oral and Maxillofacial Surgery 50: 1196–1206

Holtrop M E 1964 Enchondrale verbening in muizeribben. Een experimenteel histologisch en cytologish onderzoek. Thesis, University of Leiden, The Netherlands

Hunziker E B, Schenk R K, Cruz-Orive L-M 1987 Quantitation of chondrocyte performance in growth plate cartilage during longitudinal bone growth. Journal of Bone and Joint Surgery 69A: 162–173

Joondeph D R 1972 An autoradiographic study of the temporomandibular articulation in the growing *Saimiri sciureus* monkey. American Journal of Orthodontics 62: 272–286

Kantomaa T, Hall B K 1988a Organ culture providing an articulating function for the temporomandibular joint. Journal of Anatomy 161: 195–201

Kantomaa T, Hall B K 1988b Mechanism of adaptation in the mandibular condyle of the mouse. An organ culture study. Acta Anatomica 132: 114–119

Kember N F 1978 Cell kinetics and the control of growth in long bones. Cell and Tissue Kinetics 11: 477–485

Kember N F, Kirkwood J K 1991 Cell kinetics and the study of longitudinal bone growth: a perspective. In: Dixon A D, Sarnat B G, Hoyte D A N (eds.) Fundamentals of bone growth: methodology and applications. CRC Press, Boca Raton, pp. 157–184

Koski K 1968 Cranial growth centers: facts or fallacies? American Journal of Orthodontics 54: 566–583

Koski K 1981 Mechanisms of craniofacial skeletal growth. In: Barrer H G (ed.) Orthodontics—the state of the art. University of Pennsylvania Press, Philadelphia, pp. 209–222

Koski K 1985 Reflexions on craniofacial growth research. Acta Morphologica Neerlando-Scandinavica 23: 357–368

Koski K, Mason K E 1964 Growth potential of transplanted components of the mandibular ramus of the rat. II. Suomen Hammaslääkäriseuran Toimituksia 60: 209–218

Koski K, Rönning O 1965 Growth potential of transplanted components of the mandibular ramus of the rat. III. Suomen Hammaslääkäriseuran Toimituksia 61: 292–297

Koski K, Rönning O 1970 Growth potential of intracerebrally transplanted cranial base synchondroses in the rat. Archives of Oral Biology 15: 1107–1108

Kylämarkula S, Rönning O 1979 Transplantation of a basicranial synchondrosis to a sutural area in the isogeneic rat. European Journal of Orthodontics 1: 145–153

Kylämarkula S, Rönning O 1983 Morphogenic potential of autogenous costal cartilage transplanted into the interparietal suture area of the rat. Journal of Neurosurgery 58: 755–759

Lacroix P 1951 The organization of bones. J & A Churchill, London

Luder H U, Leblond C P, von der Mark K 1988 Cellular stages in cartilage formation as revealed by morphometry, radioautography and type II collagen immunostaining of the mandibular condyle from weaning rats. American Journal of Anatomy 182: 197–214

Meikle M C 1973 *In vivo* transplantation of the mandibular joint of the rat; an autoradiographic investigation into cellular changes at the condyle. Archives of Oral Biology 18: 1011–1020

Meikle M C 1975 The influence of function on chondrogenesis at the epiphyseal cartilage of a growing long bone. Anatomical Record 182: 387–400

Moss M L 1962 The functional matrix. In: Kraus B S, Riedel R A (eds.) Vistas in orthodontics. Lea & Febiger, Philadelphia, pp. 85–98

Moss M L 1981 Genetics, epigenetics, and causation. American Journal of Orthodontics 80: 366–375

Öberg T, Fajers C-M, Lohmander S, Friberg U 1967 Autoradiographic studies with H3-thymidine on cell proliferation and differentiation in the mandibular joint of young guinea pigs. Odontologisk Revy 18: 325–344

Oudhof H A J, van Doorenmaalen W J 1983 Skull morphogenesis and growth: hemodynamic influence. Acta Anatomica 117: 181–186

Peltomäki T 1993 Growth of the costochondral junction and its potential applicability for the reconstruction of the mandibular condyle. Thesis, University of Turku, Ser. D, Medica-Odontologica 108: 1–77

Peltomäki T, Rönning O 1991 Interrelationship between size and tissue-separating potential of costochondral transplants. European Journal of Orthodontics 13: 459–465

Peltomäki T, Rönning O 1993 Growth of costochondral fragments transplanted from mature to young isogeneic rats. Cleft Palate-Craniofacial Journal 30: 159–163

Peskin S, Laskin D M 1965 Contribution of autogenous condylar grafts to mandibular growth. Oral Surgery, Oral Medicine, Oral Pathology 20: 517–534

Petrovic A G 1984 Experimental and cybernetic approaches

to the mechanism of action of functional appliances on mandibular growth. In: McNamara J A, Ribbens K A (eds.) Malocclusion and the periodontium. Monograph No. 15, Craniofacial Growth Series, Center for Human Growth and Development, University of Michigan, Ann Arbor, pp. 313–368

Petrovic A G, Stutzmann J J 1981 A cybernetic view of facial growth mechanism. In: Kehrer T, Slongo T, Graf D, Bettex M (eds.) Long term treatment in cleft lip and palate. Hans Huber Publishers, Bern, pp. l4–57

Rönning O 1966 Observations on the intracerebral transplantation of the mandibular condyle. Acta Odontologica Scandinavica 24: 443–457

Rönning O 1971 Alterations in craniofacial morphogenesis induced by parenterally administered papain. Thesis, University of Turku, Suomen Hammaslääkäriseuran Toimituksia 67: suppl III

Rönning O, Kantomaa T 1988 The growth pattern of the clavicle in the rat. Journal of Anatomy 159: 173–179

Rönning O, Kylämarkula S 1982 Morphogenetic potential of rat growth cartilages as isogeneic transplants in the interparietal suture area. Archives of Oral Biology 27: 581–588

Rönning O, Peltomäki T 1991 Growth potential of the rat mandibular condyle as an isogeneic transplant traversing the interparietal suture. Archives of Oral Biology 36: 203–210

Rönning O, Rintala M, Kantomaa T 1991 Growth potential of the rat clavicle. Journal of Oral and Maxillofacial Surgery 49: 1176–1180

Schatten W E, Bergenstal D M, Kramer W M, Swarm R L, Siegel S 1958 Biological survival and growth of cartilage grafts. Plastic and Reconstructive Surgery 22: 11–28

Scott J H 1954 The growth of the human face. Proceedings of the Royal Society of Medicine 47: 91–100

Scott J H 1962 The growth of the cranio-facial skeleton. Irish Journal of Medical Science 488: 276–286

Strobino L J, French G O, Colonna P C 1952 The effect of increasing tensions on growth of epiphyseal bone. Surgery, Gynecology and Obstetrics 95: 694–700

Stutzmann J, Petrovic A, George D 1991 Nature and number of dividing cells and distribution of collagens type I, II and X in the medial cartilage of the clavicle during spontaneous and biomechanically modulated postnatal growth. In: Dixon A D, Sarnat B G, Hoyte D A N (eds.) Fundamentals of bone growth: methodology and applications. CRC Press, Inc., Boca Raton, pp. 95–111

Tran S, Hall B K 1989 Growth of the clavicle and development of clavicular secondary cartilage in the embryonic mouse. Acta Anatomica 135: 200–207

van Limborg J 1972 The role of genetic and local environmental factors in the control of postnatal craniofacial morphogenesis. Acta Morphologica Neerlando-Scandinavica 10: 37–47

Vinkka H 1982 Secondary cartilages in the craniofacial skeleton of the rat. Thesis, University of Turku, Proceedings of the Finnish Dental Society 78: Suppl VII

Vinkka-Puhakka H 1991 Craniofacial secondary cartilages in the hamster and rat. In: Dixon A D, Sarnat B G, Hoyte D A N (eds.) Fundamentals of bone growth: methodology and applications. CRC Press, Boca Raton, pp. 131–137

Vogl C, Atchley W R, Cowley D E, Crenshaw P, Murray J D, Pomp D 1993 The epigenetic influence of growth hormone on skeletal development. Growth, Development & Aging 57: 163–182

Ware W H, Taylor R C 1965 Replantation of growing mandibular condyles in rhesus monkeys. Oral Surgery, Oral Medicine, Oral Pathology 19: 667–669

Young R W 1959 The influence of cranial contents on postnatal growth of the skull in the rat. American Journal of Anatomy 105: 383–415