

Management of Growth Arrest with Tissue-engineered Cells

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Master of the Academy; Chairman, Chapter of Surgeons; Mrs Nina Cohen; Distinguished Guests; Ladies and Gentlemen:

Before I go on to the scientific aspects of my talk, I would like to pay tribute to Dr Yahya Cohen. Dr Cohen was born in Singapore of Jewish parents. After completing his primary and secondary education, he went on to pursue his Medical Studies and graduated from King Edward VII College of Medicine in 1947 with distinctions in medical jurisprudence, surgery and obstetrics and gynaecology. He was awarded a Queen's Scholarship for further studies in England where he obtained the Fellowship of the Royal College of Surgeons of England. While overseas, he received further training in general surgery and plastic surgery in Edinburgh and Oxford. Following his return to Singapore, he was appointed Lecturer in surgery. He subsequently headed the Government Surgical Unit and was appointed Clinical Professor and Senior Surgeon until his retirement in 1972.

In addition to his surgical headship, Dr Cohen held numerous positions of responsibility during his long and illustrious career. He was a founder member and first Scribe of the Academy of Medicine when it was instituted in 1957. Nine years later when the Chapter of Surgeons was started, he was elected the first Chairman. He became the Master of the Academy of Medicine from 1968 to 1970. Dr Cohen was President of the Singapore Medical Association from 1961 to 1962 and was the first Chairman of the Committee of Surgery of the School of Postgraduate Medical Studies, University of Singapore, an office which he held from 1967 to 1977. In addition, he was also the President of the Singapore Medical Council in 1972.

Apart from his administrative abilities, Dr Cohen commanded great respect from all his peers and his students as a great clinician, a meticulous surgeon, a caring doctor and an excellent teacher. He is well known to be a firm disciplinarian and has been an advocate of ethical and safe practices in surgery.

Although I did not have the privilege of working with Dr Cohen, I was honoured one day by his presence in one of our departmental teaching sessions when I presented a talk on "Gait Analysis". At that time, Dr Cohen had been retired

for more than 10 years, but his attendance and active participation in the discussion following the talk exemplified his continued involvement with academic medicine.

Dr Cohen is indeed a person who is a credit to our profession, a person who has dedicated his life to the art and practice of surgery and the unselfish care of patients. Men like him are few and far between and I feel extremely honoured and privileged to have known him and to be part of the medical community that he belongs to.

The Growth Plate

As an orthopaedic surgeon, treating children, I have a particular interest in the growth plate. This is an area towards the ends of long bones, made up of special cells arranged in columns that contribute to the longitudinal growth of the bone. Damage to the growth plate can thus give rise to problems with growth. As the growth plate is very near the ends of long bones, injuries to the growth plate were originally construed as a dislocation of the joint. It was Pare in 1619 who recognised that the injury was an epiphyseal separation rather than a dislocation. Subsequently, Ollier in 1867 described the cleavage plane between the epiphysis and the metaphysis. Physeal fractures account for between 15% to 20% of all injuries in children. They are more common in males with the peak incidence in adolescence. There are many different classifications of physeal injuries, but the most commonly accepted classification is that of Salter and Harris¹ which describes 5 types of growth plate injuries. Mercer Rang² has more recently added a 6th type which involve injuries of the perichondrial ring.

Growth Arrest

Most physeal fractures do not result in growth arrest. Salter and Harris's types 3, 4 and 5 are the ones shown to have a higher incidence of damage to the physis resulting in subsequent growth problems in the long bone. Growth arrest can be classified as partial or complete. A complete growth arrest is rare and will usually result in cessation of growth leading to leg length discrepancy. It is more common to have a partial growth arrest which can lead to angular deformity as well as some loss in growth in length. Partial growth arrest can be classified as type 1: peripheral, type 2:

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central and type 3: combined. Type 1 is the most common, comprising 60% of all partial growth arrest. Types 2 and 3 occur 20% of the time respectively. The main causes of growth arrest are either trauma or sepsis. The most severe growth arrest occurs from infections especially in the neonatal period and this can result in very severe leg length discrepancy as well as angular deformities of the leg.

Management of Partial Growth Arrest

Traditionally, there are 2 main methods of treating growth arrest. In the growing child, Langenskiöld³ has popularised the method of resection of the bony bridge and using a fat graft as an interposition material to prevent further formation of the bridge. This technique has been shown to be useful in instances where the bony bridge occupies less than 30% of the entire growth plate. Alternative methods would involve serial osteotomies to correct angular deformity. In the child nearing maturity, an osteotomy would be advocated. When there is an extensive involvement of the growth plate with peripheral as well as central involvement such as in cases of sepsis, combinations of these methods may have to be used. More recently, there has also been a technique described of involving slow distraction of the growth plate termed chondrodiastasis or hemichondrodiastasis for correction of angular deformity.

Experimental Studies on the Growth Plate

I began studies on the growth plate in 1987. Using immature rabbits, an experimental model for growth arrest was devised by excising the medial half of the proximal tibial physis. This inevitably resulted in varus deformity of the tibia. Histological studies confirmed the formation of a bony bridge within 2 weeks of excision of the growth plate. In my early studies, a piece of the iliac apophysis was harvested and used as a physeal substitute. Three weeks after the initial surgery when the physis was excised, the proximal tibia was again reopened and the bony bridge excised. A piece of the iliac apophysis was then shaped to fit the defect from which the bony bridge was excised. When the rabbit was followed up, it was found that the tibia did not develop the severe varus deformity that it otherwise would have. Histological studies showed that the transplanted physis from the iliac apophysis remained intact in the physeal defect and seemed to be contributing to the growth of the tibia.⁴ Further experiments were performed to compare use of the iliac apophysis to fat and silastic interposition material. The studies showed that the physeal transfer provided the best result in terms of prevention of angular deformity.⁵ However, the angular deformity was not totally prevented and there was still residual varus deformity with loss in length of the bone.

To address the problem of residual deformity and longitudinal growth, a special distraction device was made

and an experiment involving hemichondrodiastasis of the proximal tibia physis was performed in the same rabbit model. This study showed that with slow distraction, the angular deformity and loss of longitudinal growth could be corrected. In addition, it also showed that when the bony bridge occupied a small area (less than 30%) of the entire growth plate, distraction alone was successful without having to excise the bony bridge.⁶

Tissue Engineering Research

Drawing from the experience of previous studies, further research was carried out using tissue engineering techniques starting about 5 years ago. I felt that although physeal transfers from the iliac apophysis gave promising results, it did not correct the deformity completely. My hypothesis at that time was that if cartilage cells could be cultured from the iliac apophysis and transferred into the physeal defect, the transferred cells could contribute to more normal physeal growth. Chondrocytes were harvested from the iliac apophysis and grown in tissue culture (Fig. 1). Using the same experimental model of growth arrest in the proximal tibia, the chondrocytes were then transferred into the physeal defect after excision of the bony bridge. Agarose was used as the carrier for the cells. A control group of rabbits received agarose only without cells in the physeal defect. The results showed that the transfer of agarose alone resulted in severe angular deformity of the tibia. When agarose was transferred with cultured chondrocytes, the angular deformity did not develop (Fig. 2). Histological studies showed that the chondrocytes were able to lineup in a columnar fashion within 2 weeks of transfer and by 6 to 8 weeks, a new growth plate had developed which was indistinguishable from a normal growth plate⁷ (Fig. 3). To ensure that the cells in the new growth plate were actually derived from the cultured cells, the chondrocytes were labelled with 5 carboxy fluorescein diacetate succinylidyl

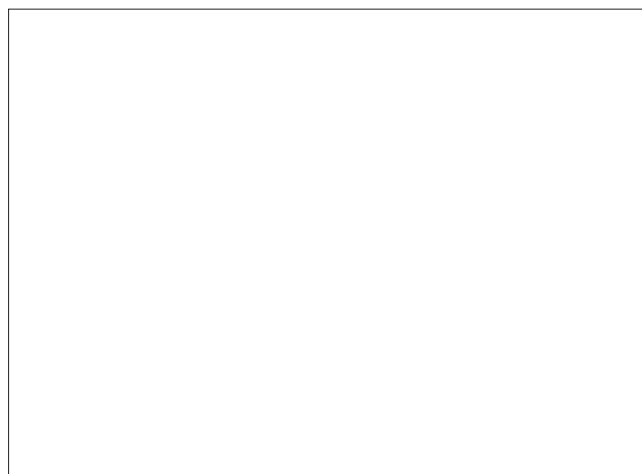


Fig. 1. Chondrocytes in tissue culture before passage.

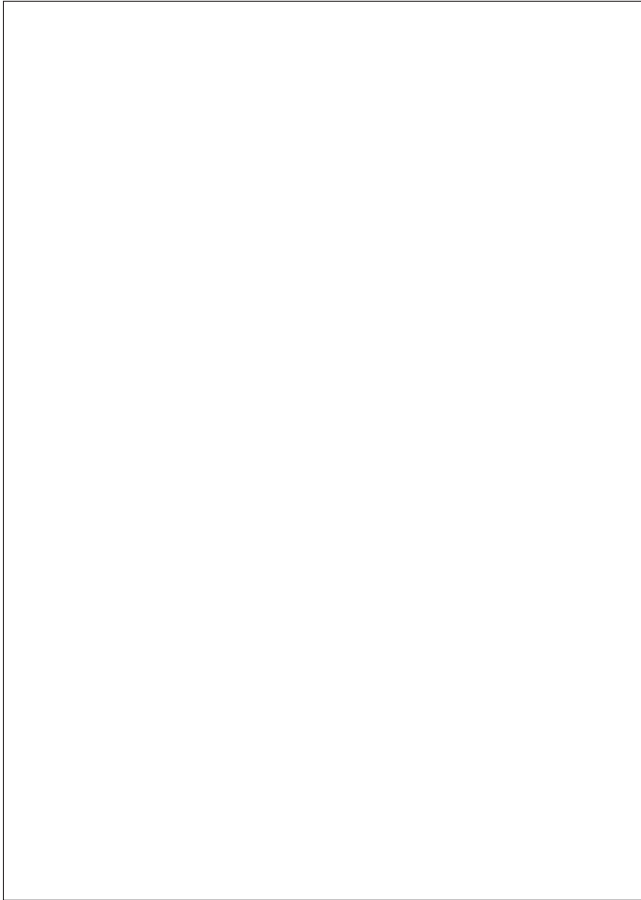


Fig. 2. X-rays showing deformity of tibia due to growth arrest after transfer of agarose alone (left) compared with transfer of cells in agarose (right), resulting in prevention of growth arrest and deformity.

ester (CFSE) (Fig. 4). This confirmed that the transferred cells contributed to the new growth plate. Although there was very little angular deformity in the experimental animals, there was still some residual limb length discrepancy.

Currently our Tissue Engineering Laboratory is culturing mesenchymal stem cells and we are using these cells for transfer in a similar experimental model. Preliminary results are very encouraging in terms of prevention of angular deformity as well as contribution to growth in length of the bone. With the same technology for tissue culture, we are also investigating the use of these cells for repair of defects in articular cartilage. Our tissue engineering research group will be investigating the use of growth factors as well as developing better carriers and scaffolds for cells. This is a very exciting area in research and we hope to be able to contribute to further understanding in the area of repair of damaged cartilage with biological methods.

I would like to acknowledge Dr Chen Fen, Miss Julie Chan and Dr G X Gao for their contributions to this research. Thank you.

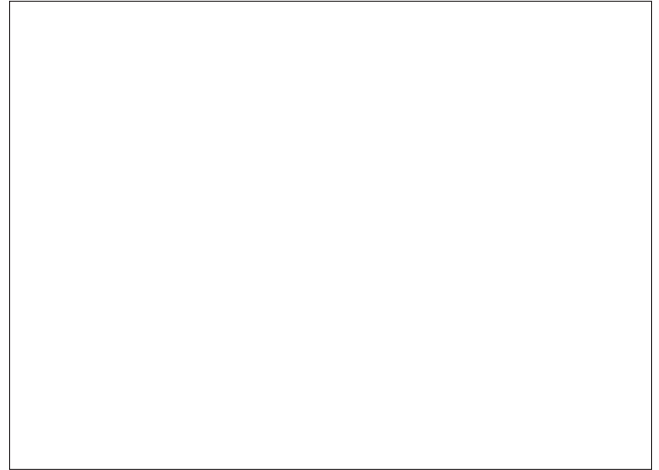


Fig. 3. Histological section through physal defect showing normal growth of cells after transfer.

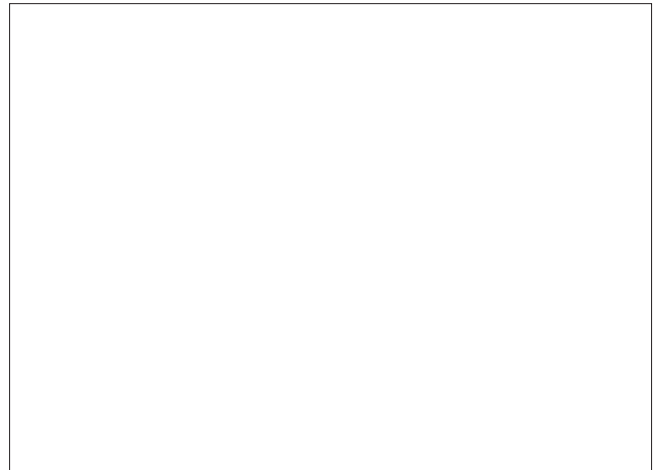


Fig. 4. Histological section with CFSE stain showing that cells in physis are transferred chondrocytes.

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