**NATURAL HISTORY: MULTIPLE EPPHYSEAL DYSPLASIA**

(Note: the following summary of the natural history of Multiple Epiphyseal Dysplasia is neither exhaustive nor cited. It is meant to provide a guideline for the kinds of problems that may arise in those with this disorder, and particularly to help clinicians caring for a recently diagnosed child. For specific questions or more detailed discussions, feel free to contact the Midwest Regional Bone Dysplasia Clinic at the University of Wisconsin - Madison [608 262 9722; fax - 608 263 3496)

**MEDICAL ISSUES AND PARENTAL CONCERNS TO BE ANTICIPATED**

**INTRODUCTION:** Unlike many bone dysplasias, multiple epiphyseal dysplasia may be delayed in presentation and frequently diagnosis is not made until an individual is between 2 and 10 years of age. Diagnosis is sometimes even delayed beyond these ages. First indicators of the presence of this disorder are waddling gait, difficulties running, limping, joint stiffness, joint pain and/or subtle slowing of growth velocity.

Multiple epiphyseal dysplasia is a descriptive diagnosis, simply implying that an individual has an intrinsic bone dysplasia limited to the ends (epiphyses) of the long bones and with little or no spine involvement. In general, there is profound delay in epiphyseal maturation and deformity of epiphyses. The best described of the various forms of multiple epiphyseal dysplasia is sometimes termed the Fairbank type. Most of the information outlined here is most specifically applicable to those with this type of multiple epiphyseal dysplasia.

**PROBLEM: GROWTH**

**EXPECTATIONS:** Initial growth in infancy and early childhood is often normal. Minimal to moderate short stature is usual, with adult heights ranging from about 135 cm to 155 cm. Head growth is normal.

**MONITORING:** There are no growth charts available. Plotting linear growth on regular growth standards may provide some guide to whether growth velocity is being maintained.

**INTERVENTION:** No known treatment. Growth hormone etc. is not likely to be effective since this disorder is secondary to intrinsic abnormality of bone growth. Limb lengthening has been used occasionally but remains controversial.
**Problem: Hips**

**Expectations:** Hip pain is often the first presenting symptom. Stiffness, abnormal gait (waddling) and limping may also be the first recognized characteristics in early childhood. In addition to the intrinsic and constant abnormalities of the hip, avascular necrosis (Legg-Perthes disease) develops in a substantial minority. Hip degeneration and premature osteoarthritis is nearly uniform often arising in early adolescence. Many will have total hip replacement, often in the 30s or 40s.

**Monitoring:** Radiologic assessment with symptoms.

**Intervention:** Limitations of repetitive weight bearing activities and other activities that result in repetitive stress on the hips, such as rope jumping, trampoline use etc., can slow degenerative arthritic change. If avascular necrosis develops this is treated with traditional methods (a period of non-weight-bearing and physical therapy followed by abduction bracing). Use of a motorized scooter for long distance mobility is warranted whenever osteoarthritic problems become severe - sometimes as early as adolescence.

**Problem: Other Large Joint Symptoms**

**Expectations:** More generalized osteoarthritis is not uncommon. This is particularly common in the knees and the shoulders. As with Legg-Perthes developing in the hips, osteochondritis dessicans may develop in the knees.

**Monitoring:** Clinical monitoring. Radiologic assessment may help predict the severity of problems that can be expected — for example, the shape of the proximal humerus and humeral head is an excellent sign to assess likelihood of and severity of shoulder arthritis later in life; likewise the degree of fragmentation of the femoral head allows prediction in late childhood of how severe osteoarthritic changes will become in the ensuing decades.

**Intervention:** The usual treatments for osteoarthritis are applicable, but may need to commence in adolescence and young adult life.

**Problem: Leg Positional Abnormalities**

**Expectations:** Beginning after orthograde weight bearing, nearly all develop some knee and leg position abnormality, but these are usually relatively mild. Either varus deformity (bowleg) or valgus deformity (knockknee) may develop. Progressive deformity may arise and may be sufficiently severe in some older children to warrant surgical intervention.

**Monitoring:** Clinical monitoring for alignment, development of chronic knee pain, limitation of ambulation (usually secondary to pain).

**Intervention:** Surgery should be reserved for those with severe and symptomatic mal-alignment.
**Problem: Small Joint Changes**

**Expectations:** Hands are short with particularly short fingers. There is often mild generalized hypermobility.

**Monitoring:** Function is usually fine, but some individuals may experience moderate fine motor difficulties or fatigue secondary to efforts to stabilize intrinsically unstable small joints.

**Intervention:** Usually none. Minor adaptations for fine motor activities in school may be needed.

**Problem: Adaptive**

**Expectations:** In general short stature is not so severe that major environmental adaptations are needed.

**Monitoring:** Assess for age appropriate needs.

**Intervention:** School adaptations, stools, etc. if needed.

**Genetics and Molecular Biology**

Multiple epiphyseal dysplasia is relatively common, arising in around 1 in every 10,000 individuals. Multiple epiphyseal dysplasia is usually caused by an autosomal dominant gene abnormality. This means that an adult with this disorder will have a 50% chance to pass this poorly functional gene on to each child. Infrequently an individual with this disorder will be born to average statured parents. It is not yet known whether this is because there are autosomal recessive forms of multiple epiphyseal dysplasia or if this arises because of a new chance change (mutation) in only the single egg or single sperm giving rise to the affected individual. Given the complexities of accurate diagnosis of subtypes of this disorder, diagnostic evaluation in a bone dysplasia center prior to any counseling regarding recurrence risk is essential.

Thusfar, changes in at least two different genes are known to be capable of causing multiple epiphyseal dysplasia. At least some instances of multiple epiphyseal dysplasia arise secondary to mutations in a gene which codes for Cartilage Oligomeric Matrix Protein (the same gene that is involved in a similar but more severe bone dysplasia called Pseudoachondroplasia). In other families multiple epiphyseal dysplasia arises because of mutation within one type IX collagen gene (Col9A2). Thusfar, there is not enough information available to know if finding which gene is involved is of prognostic benefit.