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SCIENTIFIC ARTICLE

The developmental spectrum of proximal radioulnar synostosis

Alison M. Elliott · Lisa Kibria · Martin H. Reed

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Abstract
Objective Proximal radioulnar synostosis is a rare upper limb malformation. The elbow is first identifiable at 35 days (after conception), at which stage the cartilaginous anlagen of the humerus, radius and ulna are continuous. Subsequently, longitudinal segmentation produces separation of the distal radius and ulna. However, temporarily, the proximal ends are united and continue to share a common perichondrium. We investigated the hypothesis that posterior congenital dislocation of the radial head and proximal radioulnar fusion are different clinical manifestations of the same primary developmental abnormality.
Materials and methods Records were searched for "proximal radioulnar fusion/posterior radial head dislocation" in patients followed at the local Children's Hospital and Rehabilitation Centre for Children. Relevant radiographic, demographic and clinical data were recorded. Ethics approval was obtained through the University Research Ethics Board.
Results In total, 28 patients met the inclusion criteria. The majority of patients (16) had bilateral involvement; eight with posterior dislocation of the radial head only; five had posterior radial head dislocation with radioulnar fusion and two had radioulnar fusion without dislocation. One patient had bilateral proximal radioulnar fusion and posterior dislocation of the left radial head. Nine patients had only left-sided involvement, and three had only right-sided involvement.The degree of proximal fusion varied, with some patients showing 'complete' proximal fusion and others showing fusion that occurred slightly distal to the radial head: 'partially separated.' Associated disorders in our cohort included Poland syndrome (two patients), Cornelia de Lange syndrome, chromosome anomalies (including tetrasomy X) and Cenani Lenz syndactyly.
Conclusion The suggestion of a developmental relationship between posterior dislocation of the radial head and proximal radioulnar fusion is supported by the fact that both anomalies can occur in the same patient. Furthermore, both anomalies can be seen in different patients with the same genetic diagnosis, further supporting the notion that these defects are developmentally related. Posterior dislocation of the radial head and radioulnar fusion are considered to be related primary developmental anomalies of radioulnar differentiation/segmentation. We speculate that the eventual specific defect of this spectrum is influenced by very subtle differ-

A. M. Elliott
Winnipeg Regional Health Association Program of Genetics and Metabolism, University of Manitoba,
Winnipeg, MB, Canada

A. M. Elliott · M. H. Reed
Department of Paediatrics and Child Health,
University of Manitoba,
Winnipeg, MB, Canada

A. M. Elliott · M. H. Reed
Department of Biochemistry and Medical Genetics,
University of Manitoba,
Winnipeg, MB, Canada

L. Kibria
Department of School of Medical Rehabilitation,
University of Manitoba,
Winnipeg, MB, Canada

M. H. Reed
Department of Diagnostic Imaging, University of Manitoba,
Winnipeg, MB, Canada

A. M. Elliott (✉)
WRHA Program of Genetics and Metabolism,
Departments of Paediatrics and Child Health,
Biochemistry and Medical Genetics, University of Manitoba,
Winnipeg, MB, Canada
e-mail: aelliott@hsc.mb.ca

ences in developmental timing. This is in contrast to patients with transverse forearm defects who can also display radial head dislocation but in an anterior or lateral direction. This direction of dislocation is seen when an abnormal force is exerted on a normally formed radial head later in development or postnatally in disorders such as multiple osteochondromatosis and various mesomelic dysplasias, or as a result of trauma.

Keywords Radioulnar synostosis · Fusion · Radial head dislocation · Syndrome

Introduction

Proximal radioulnar synostosis (RUS) is a rare upper limb malformation. The elbow is first identifiable at 35 days (after conception), at which stage the cartilaginous anlagen of the humerus, radius and ulna are continuous. Subsequently, longitudinal segmentation produces separation of the distal radius and ulna, but briefly, the proximal ends are united and continue to share a common perichondrium [1]. We investigated the hypothesis that posterior congenital dislocation of the radial head and proximal radioulnar fusion are different clinical manifestations of the same developmental abnormality.

Materials and methods

Records were searched for "proximal radioulnar fusion/posterior radial head dislocation" in patients followed at the local Children's Hospital and Rehabilitation Centre for Children. Relevant radiographic, demographic and clinical data were recorded. Ethics approval was obtained through the University Research Ethics Board. The literature was searched for "radioulnar synostosis/fusion", and relevant publications were examined for classifications and proposed mechanisms of RUS.

Results

In total, 28 local patients met the inclusion criteria. The majority of patients (16) had bilateral involvement. Of the bilateral cases, eight had posterior dislocation of the radial head only; five had posterior radial head dislocation in association with radioulnar fusion and two had radioulnar fusion without dislocation. One patient had bilateral proximal radioulnar fusion and posterior dislocation of the left radial head. Twelve patients had unilateral involvement. Seven patients had radial head dislocation; three had radioulnar fusion, while two had radial head dislocation with radioulnar fusion. Nine patients had only left-sided involvement, and three had only right-sided involvement. The degree of proximal fusion varied, with some patients showing 'complete' proximal fusion (Fig. 1) and others with fusion occurring slightly distal to the radial head: 'partially separated' (Fig. 2a, b).

There were 12 boys and 16 girls in the study.

The majority of our patients had isolated RUS. Associated disorders in our cohort included Poland syndrome (two patients) (Fig. 3), Cornelia de Lange syndrome (two patients), Cenani Lenz syndactyly (CLS), Noonan syndrome and nail patella syndrome. Chromosome anomalies included Tetrasomy X (Fig. 4) and 11q23 deletion. Patients with developmental delay, juvenile rheumatoid arthritis (with unilateral congenital radioulnar synostosis) and one patient with an unknown syndrome (Fig. 5) were also included.

Discussion

Congenital synostosis of the proximal radius and ulna is an uncommon malformation of the upper extremity and was first described by Sandifort in 1793 [2]. This anomaly can be seen in a number of syndromes and skeletal dysplasias, but it is most often found sporadically as an isolated finding. Its association with X chromosome anomalies is well known. It is often accompanied by distal limb anomalies, including oligodactyly and carpal bone abnormalities.

Development

The upper limb bud arises from the body wall at approximately 26 days of development (after conception), and the elbow is first discernable at 35 days. At this stage there are three connected cartilaginous anlagen present, which will eventually develop into the humerus, radius and ulna. Soon afterwards, longitudinal segmentation produces separation of the distal radius and ulna. However, briefly, their proximal ends are united and share a common perichondrium [1]. Abnormal genetic or environmental factors operating at this time in development could interrupt subsequent proximal radioulnar joint morphogenesis [3, 4]. Simmons et al. proposed in 1983 that such interference would allow for later ossification of the entire proximal cartilaginous model and produce complete bony synostosis. If joint development continued before the developmental arrest occurred, this could lead to a smaller area of coalition and the presence of a rudimentary radial head [2]. These two scenarios also represent related primary anomalies of radioulnar differentiation/segmentation. The final specific defect of this spectrum is influenced by subtle differences in developmental timing.

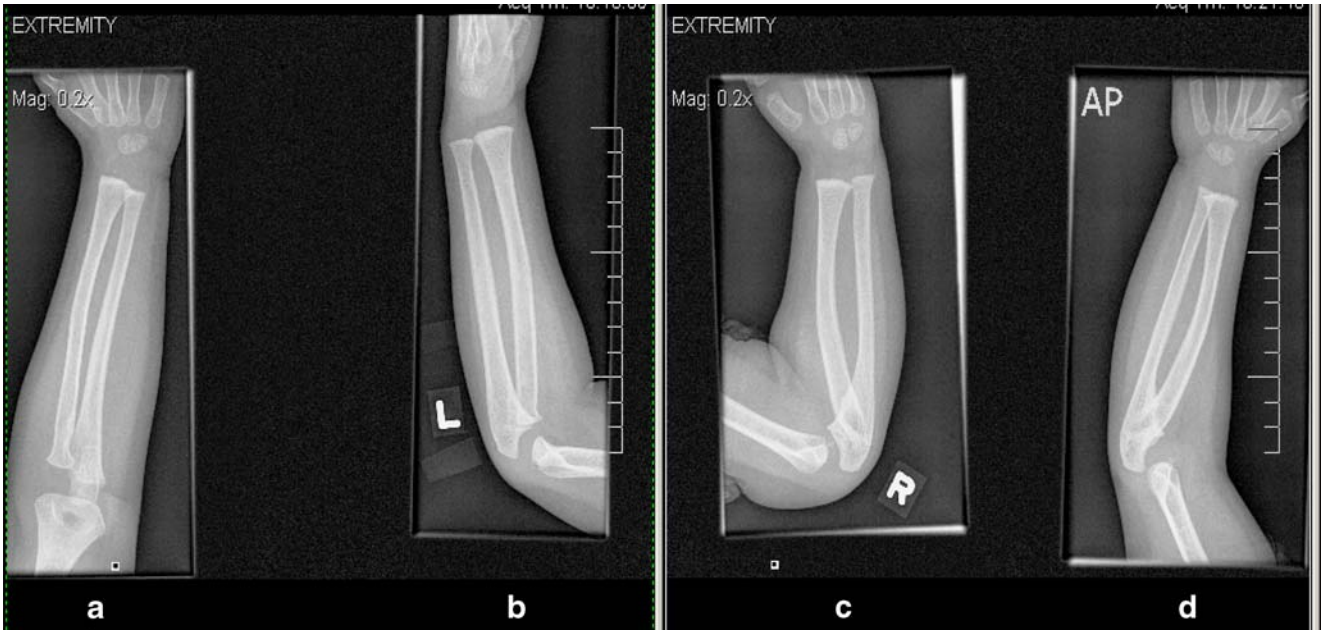


Fig. 1 A 3.5-year-old-boy with isolated limb finding. *Panels a and b* left upper extremity. There is no fusion and no posterior subluxation. *Panels c and d* right upper extremity. There is proximal fusion up to the level of the radial head, with posterior dislocation. *L* left, *R* right, *AP* antero-posterior view

Classifications

Different classifications of radioulnar synostosis have been proposed. Wilkie proposed two forms [5]. In type I, also referred to as true radioulnar synostosis, there is a proximal smooth fusion of approximately 2–6 cm, between the ulna and radius, and the radial head is absent. In type II there is fusion distal to the proximal radial epiphysis, in association with congenital dislocation of the radial head.

Cleary and Omer proposed four distinct radiographic patterns [6]. In type I the synostosis does not involve bone and is associated with a reduced, normal-appearing, radial head; type II is represented by a visible osseous synostosis but is associated with otherwise unremarkable findings; type III is osseous synostosis with a hypoplastic and posteriorly dislocated radial head, and type IV is represented by a short osseous synostosis with an anteriorly dislocated radial head that is often 'mushroom shaped.'

The association with RUS and morphologic findings of the radial head as characterized in types III and IV by Cleary and Omer is supported by another group. Yammine and colleagues proposed a new radiologic classification of RUS based on the fact that the degree of fusion of the synostosis was positively correlated with the presence of a morphological abnormality of the radial head (hypertrophy or hypoplasia) in their radiographic analysis of 30 patients (38 forearms) [7]. They proposed that such an abnormality of the radial head may be predictive of early development of a segmentation defect, resulting in a more marked degree of fusion in the synostosis.

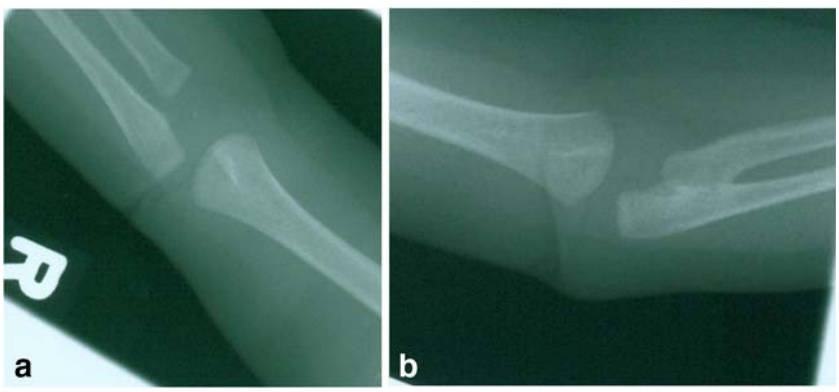


Fig. 2 Two-month-old boy. He presented clinically with limited extension of the left elbow. Radiograph of the right elbow (*R*) is normal (**a**). The left elbow shows posterior dislocation and proximal fusion distal to the radial head ('partially separated') (**b**)

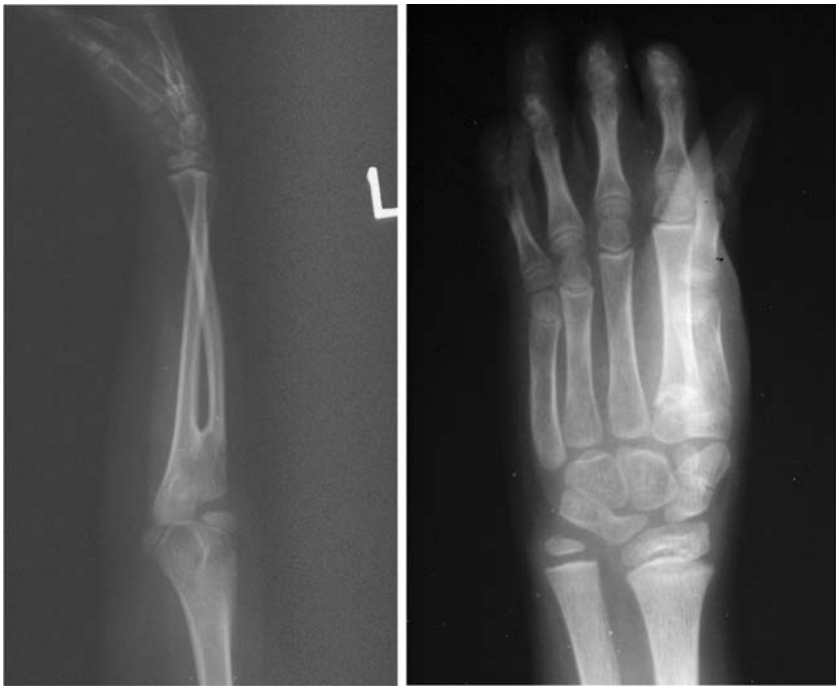


Fig. 3 Girl with Poland syndrome at 9 years 6 months. The left extremity (*L*) is affected. There is proximal radioulnar fusion ('complete') with distinctive carpal abnormalities. There is decreased bone age of all bones, scaphoid–trapezium fusion, hypoplastic trapezoid and decreased carpal height. The right extremity was normal

Etiology

Familial cases of isolated RUS tend to follow autosomal dominant inheritance and show bilateral involvement and a bias for affected boys. The patients in our cohort with isolated RUS did not have a known positive family history. A large family with autosomal dominant RUS was reported in the early literature [8]. The family reported by Spritz had three affected boys and one girl [9]. Rizzo and colleagues reported seven cases of congenital RUS—five were in the same family. In the familial cases the anomaly was inherited as an autosomal dominant trait [10].

The developmental gene(s) responsible has not been identified in isolated RUS, but mutations in the homeobox A11 (HOXA11) gene resulting in autosomal dominant RUS with amegakaryocytic thrombocytopenia in two pedigrees have been reported [11]. Not all patients with the gene mutation demonstrated marrow failure. The HOX genes are critical developmental genes in limb development [12–14].

The association of RUS and chromosome anomalies is well known. In our series one patient had tetrasomy X, while another had a deletion in chromosome 11. In their review, Pfeiffer and Santelmann discussed this association with chromosome 18 anomalies, trisomy 21, and polysomy X (in both male and female patients with supernumerary X chromosomes) [15]. Boys with supernumerary Y chromosomes have also been reported with RUS [16–18] in addition to more recent articles of Y chromosome anomalies and RUS [19, 20].

Series studies

There is no consistency in the literature regarding unilateral versus bilateral involvement in series studies of RUS. In our cohort 16 patients had bilateral involvement and 12 had

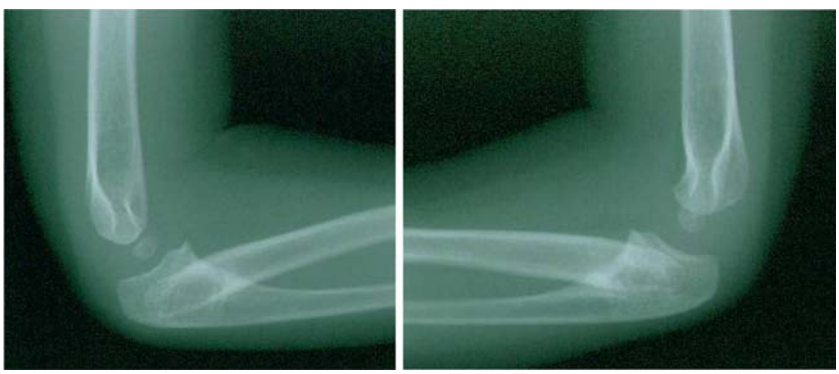
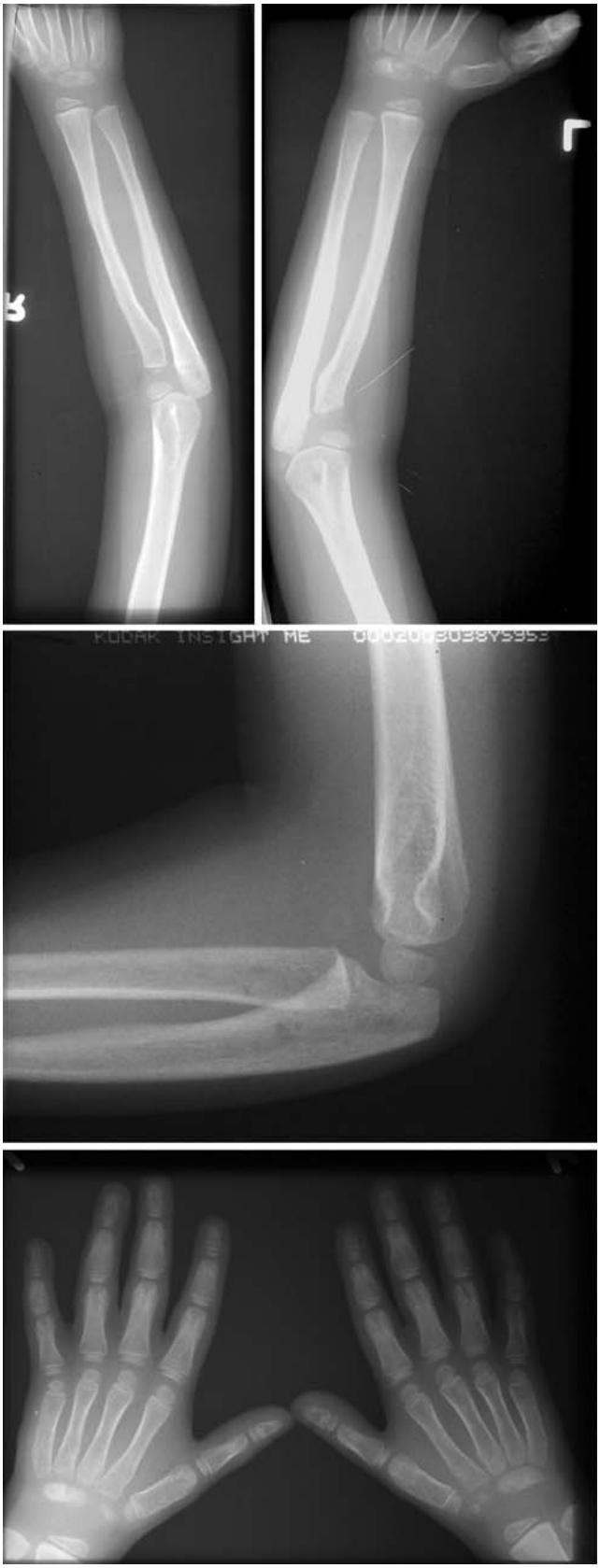


Fig. 4 Female patient with tetrasomy X syndrome (48, XXXX) at 4 years of age. She has bilateral proximal radioulnar fusions just distal to the radial head ('partially separated'), with posterior dislocation



◀ **Fig. 5** Female patient 4 years and 2 months old. She has short stature and multiple dysmorphic features. Chromosomes were normal (46, XX). The right elbow is normal. The left elbow shows mild posterior subluxation of the radial head. The epiphysis of the left radial head is evident. A closer view of the left elbow shows the subluxation. This patient also has unusual hand findings, with bilateral fusions of the capitate and hamate carpal bones. The metacarpals are thickened

unilateral involvement. With respect to gender, larger series tend to show a male bias. In our study there were more girls than boys (16 versus 12).

Simmons et al. studied 33 patients [2]. Nineteen had bilateral involvement and 14 had unilateral involvement. Of the unilateral cases, nine involved the right arm and five involved the left extremity. Of the total 33 patients, 19 were male and 14 were female. Associated syndromes were not mentioned, but there was associated organ system involvement in 11 patients and included musculoskeletal, cardiovascular, thoracic, central nervous system, renal and gastrointestinal involvement. Only one patient had a positive family history.

Cleary and Omer examined 23 patients with 36 cases of congenital proximal RUS [6]. Ten patients had unilateral involvement and 13 bilateral involvement. Eight patients were female and 15 were male. Associated genetic syndromes were not discussed, but no patients had ipsilateral congenital anomalies.

Bauer and Jonsson reported on three patients–two female and one male. All appeared to have isolated RUS. Two patients had unilateral involvement and one patient had bilateral involvement [21].

Yammine and colleagues performed a clinical and radiographic study of patients with RUS [7]. In their clinical study of 37 patients, 26 were male and 11 were female. Twenty-five cases had unilateral involvement and 12 had bilateral involvement. Six of the 37 patients had multiple malformations (including two patients with Larsen syndrome and one with Poland syndrome). Five patients had an associated congenital anomaly. Nineteen patients had no detectable associated anomaly or positive family history. In their radiographic analysis of 38 forearms, the authors studied the extent of the synostosis, whether the fusion was fibrous or osseous, and associated anomalies on X-ray, including dislocation and hypotrophy of the radial head, and discovered that the degree of fusion of the synostosis was positively correlated with the presence of a morphological abnormality of the radial head (hypertrophy or hypoplasia).

Farzan et al. studied 11 cases of RUS in 2002 [22]. In five patients the RUS was syndromic—multiple synostosis in four and Poland syndrome in one. Gender was mentioned for only ten patients (six female and four male).

Mechanisms

The notion of a developmental relationship between posterior dislocation of the radial head and proximal

radioulnar fusion is supported by the fact that both anomalies can occur in the same patient. Further evidence is shown by the fact that some individuals with Cenani Lenz syndactyly (a presumed autosomal recessive entity) can have complete radioulnar fusion, while others may only show posterior dislocation of the radial head (the latter was the case in our patient). Of the two patients with Poland syndrome in our cohort, one had proximal radioulnar fusion, while the other showed posterior radial head dislocation, emphasizing the importance of proper vascularization for normal development and proper separation of the radius and ulna, and further supporting the idea that these findings are pathogenetically related. We have recently shown the importance of adequate vascularization with respect to carpal development, as carpal fusions are not uncommon in Poland syndrome [23].

Individuals with transverse deficiency of the forearm show a distinctly different phenotype with respect to the elbow. Because the proximal radial epiphysis is still present in these patients, the radius may grow relatively more than the ulna, distal to the elbow. Since these bones are presumably tethered by a residual interosseous membrane, the greater differential growth of the radius can explain the bowing of both the radius and ulna that can be seen in some of these patients as well as the frequent dislocation of the radial head in an anterior or lateral direction [24], which is the usual direction of a dislocation when an abnormal force such as trauma or a growth disturbance causes dislocation of the radial head postnatally.

Conclusions

The suggestion of a developmental relationship between posterior dislocation of the radial head and proximal radioulnar fusion is supported by the fact that both anomalies can occur in the same patient. Furthermore, both anomalies can be seen in different patients with the same genetic diagnosis, further supporting the notion that these defects are developmentally related. For patients with synostosis, the degree of proximal fusion varied in our cohort. We speculate that the final specific defect which occurs within this spectrum of anomalies is influenced by very subtle differences in developmental timing. Some patients will show complete synostosis, while others will have a ‘partially separated’ radial head. The latter likely represents a later developmental insult (failure to separate).

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