# Disorders of cerebellar growth and development

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**Purpose of review**

This review summarizes for the pediatrician the current understanding of normal cerebellar and brainstem development, and then discusses selected malformations to highlight advances in the area. The impact of prematurity on cerebellar growth and development is then examined. The important insights provided by recent neuroimaging and genetic advances are reviewed.

**Recent findings**

Previous areas of dispute are being addressed by advances in two major areas. Advanced neuroimaging studies during fetal and postnatal life are now providing important insights into the nature of normal and abnormal development of the brainstem and cerebellum. These powerful new techniques for defining morphology *in vivo*, together with major advances in genetics, are accelerating our understanding of genotype–phenotype relationships. Conversely, the ability to link early brain injury to subsequent cerebellar development has challenged previous understanding of the distinction between acquired and primary dysgenesis, presumed to be genetic in origin.

**Summary**

The synthesis of a rational and clinically useful classification of posterior fossa malformations has been elusive. Recent developments promise to resolve ongoing disputes that have delayed progress. However, these insights into disturbed structural development demand rigorous examination of their long-term functional significance and caution before their prognostic significance is applied clinically.

**Keywords**

cerebellum, development, posterior fossa, prematurity

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**Abbreviations**

| | |
|---|---|
| **DWM** | Dandy–Walker malformation |
| **MRI** | magnetic resonance imaging |
| **PCH** | pontocerebellar hypoplasia |


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## Introduction

Advances in our understanding of posterior fossa malformations have been impeded by ongoing controversy into the underlying mechanisms and by inconsistent application of diagnostic criteria. This has in turn prevented the development of rational and universally accepted classification schemes and, therefore, the acquisition of reliable prognostic data. In recent years, increasingly sophisticated neuroimaging capabilities in the infant, and more recently in the fetus, have provided exciting insights into the range of normal and abnormal development of posterior fossa structures. Equally exciting has been the surge in understanding of the genetic basis of many of these lesions.

Previous classification schemes for posterior fossa dysgeneses have utilized a pattern-recognition approach of the morphology, often combined with the presumed pathogenetic mechanism(s), such as hypoplasia and dysplasia [1,2,3•,4]. More recent classification schemes have utilized the presumed embryonic derivation of the anomaly based on its rhombomeric origin. Insights into the genetic mechanisms and patterns of gene expression and linkage have added another potentially important axis to the classification of these lesions [5,6•]. Despite the various contemporary frameworks that have been proposed, to date there is still no entirely satisfactory and cohesive classification scheme for posterior fossa malformations.

Before embarking on a discussion of recent developments in the area, a brief review of the current understanding of cerebellar development is warranted.

## Normal development of the cerebellum

Development of the cerebellum extends over a protracted period from 4 weeks of gestational age to 20 months of postnatal age, a period that is divided into several broad stages [7]. First, the cerebellar territory becomes defined by a thickening of the alar plate at the midbrain–hindbrain junction of the rostral neural tube. Here the so-called isthmus organizer expresses a number of genes whose products are critical for regulating the development of the future brainstem and cerebellum [6•,7].

Cellular elements of the developing cerebellum arise from a primary and secondary neuroepithelium. From the primary neuroepithelium adjacent to the fourth ventricle, cells migrate in two directions. Dorsal migration

between 8 and 13 weeks of gestational age leads to formation of the deep cerebellar nuclei and Purkinje cell layer. Dorsolateral migration from the primary neuroepithelium starts at 6 weeks of gestational age and forms the lateral rhombic lips, from whence a second wave of migration starts around 12 weeks of gestational age and proceeds tangentially over the subpial surface of the developing cerebellum where it forms a secondary neuroepithelium, the external granular layer. This surface layer of the developing cerebellum is a site of vigorous neuronal proliferation. At 16 weeks of gestational age, neurons of the external granular layer begin to migrate inward and, guided by the Bergmann radial glial fibers, they traverse the Purkinje cell layer to form the internal granular layer; this process continues until 15 months of postnatal age, when the external granular cell layer finally disappears. The burst of proliferation in the premigratory cells of the external granular layer triggers the onset of cerebellar foliation, a process that continues until at least 6 months of postnatal age. Growth of the midline vermis accelerates during the third month of gestation, and is complete by 16–18 weeks of gestational age [8,9].

The transient and fragile nature of the germinal matrices makes them vulnerable to injury, similar to the better-recognized supratentorial germinal matrix-intraventricular hemorrhage. At the same time, injury to the highly mitotic precursor cells in these areas, from insults such as hemorrhage, viruses, and metabolic toxins, likely disrupts subsequent cerebellar and brainstem development [10,11].

From the lower rhombic lips, cells migrate to form certain nuclei of the developing brainstem, most notably the pontine nuclei and inferior olives. The inferior olive sends climbing fibers into the cerebellum, connecting to the Purkinje cells at 16–18 weeks of gestational age.

Recent insights into the genetic events occurring in regions such as the isthmus organizer and the rhombic lips during early development will advance our understanding of developmental anomalies of the posterior fossa, and lead to more rational and consistently applied classification schemes.

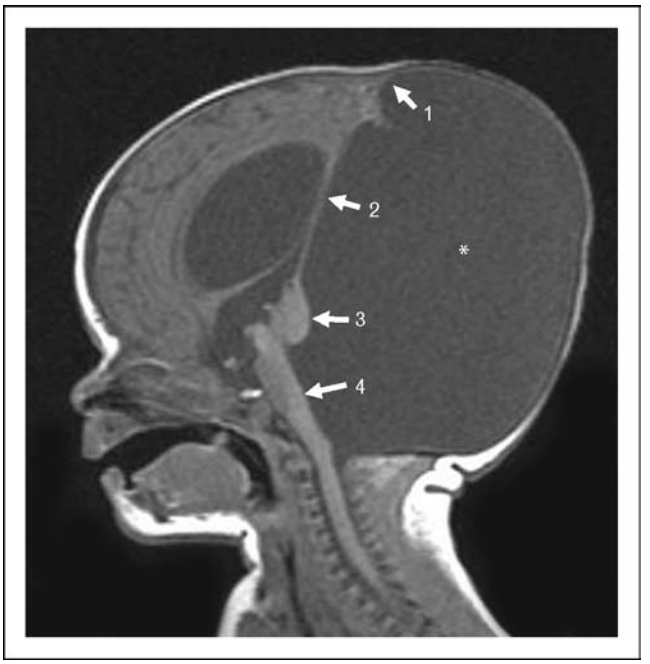
Formation of the fourth ventricle begins at around 4 weeks of gestational age with thinning of the dorsal neural-tube surface. This becomes the roof of the fourth ventricle, which is then divided by a transverse ridge of the choroid plexus into a rostral anterior membranous area (later incorporated into the choroids plexus) and a caudal posterior membranous area, within which develops first the midline foramen of Magendie and subsequently the lateral foramina of Luschka. Disturbances in these events underlie the development of the Dandy–Walker malformation, a lesion whose pathogenetic mechanism(s) remain controversial.

In summary, the protracted time course of its development exposes the cerebellum to an extended period of vulnerability during which a variety of insults are capable of derailing its normal maturational program. These issues are discussed below in the context of selected disturbances in cerebellar growth and development.

## Impaired vermian development and prominent posterior fossa cyst-like cerebrospinal fluid spaces

Within the broad spectrum of dysgenetic abnormalities in the posterior fossa, the most common lesions involve impaired vermis development associated with increased cerebrospinal-fluid spaces. There is ongoing controversy as to whether these developmental anomalies are separate entities or part of a continuum [12•]. The most striking of these anomalies is Dandy–Walker malformation (DWM), in which the enlarged cerebrospinal-fluid space results from cystic distention of the fourth ventricle, with complete or partial agenesis of the cerebellar vermis, hypoplasia of the cerebellar hemispheres, and enlargement of the posterior fossa with elevation of the torcula and anterior displacement of the brainstem; hydrocephalus develops in most cases (see Fig. 1). The pathogenetic mechanism(s) leading to the DWM remain poorly understood. How much of the morphological picture is primary dysgenesis, and how

**Figure 1 Dandy–Walker malformation**

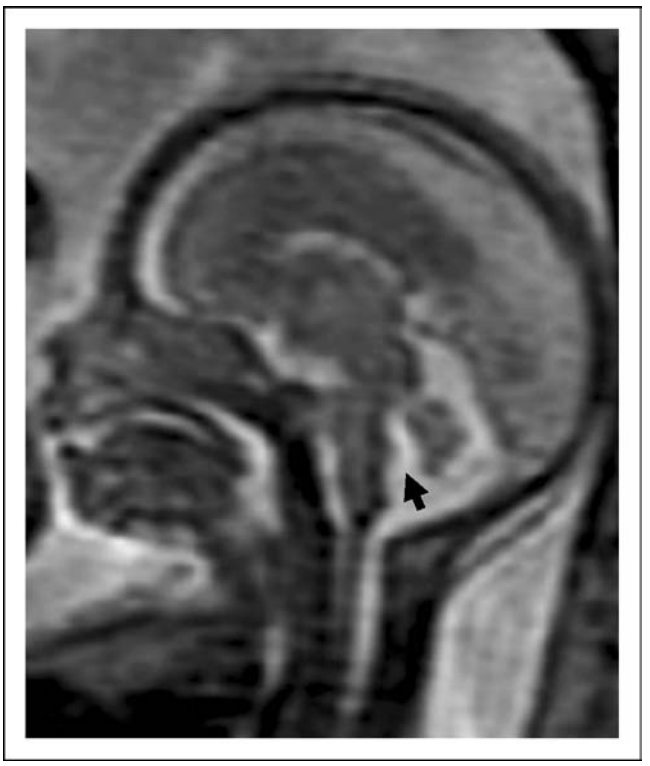



T1-weighted magnetic resonance imaging of the midline sagittal view in a full-term infant, showing elevated torcula (1) and tentorium (2), upwardly rotated hypoplastic vermis (3), anterior displacement of brainstem with hypoplastic pons (4), and massively dilated cystic fourth ventricle and posterior fossa (*).

much is secondary distortion/restriction of cerebellar growth and development by the often massively distended fourth ventricular cyst, remains unclear. In one view the cyst develops after failed incorporation of the anterior membranous area into the choroid plexus and failed or delayed development of the foramen of Magendie in the posterior membranous area. Of note, at autopsy many cases of DWM appear to have patent fourth-ventricular foramina.

An anomaly at the opposite end of this spectrum is isolated inferior vermian hypoplasia with normal cerebellar hemispheres and brainstem. This lesion appears to represent an arrested incomplete downgrowth of the vermis, leaving an enlarged midline cerebrospinal-fluid space which may be mistaken for a cystic lesion. Advances in magnetic resonance imaging (MRI) have increased the detection of more subtle forms of inferior vermian hypoplasia. The possibility of over-diagnosis of this lesion was emphasized by Limperopoulos *et al.* [13•], who showed that 32% of isolated inferior vermian hypoplasia cases diagnosed by fetal MRI in the second trimester were normal by postnatal MRI (see Fig. 2). This study raised important questions about both the sensitivity and specificity of fetal MRI, as well as possible normal variations in the time course of vermian development. The diagnostic entity of isolated inferior vermian hypoplasia continues to be inconsistently used. For example, some authors consider this lesion a normal variant, while others refer to it as the Dandy–Walker variant despite the fact that it lacks a cystic fourth ventricle and has a normal-sized posterior fossa. It is increasingly advocated that the term Dandy–Walker variant be abandoned altogether given its multiple and variable definitions, lack of specificity, and ongoing confusion with the true DWM [14]. Finally, available evidence regarding the outcome of children with isolated inferior vermian hypoplasia is conflicting, with recent studies suggesting a far more favorable outcome [13•] than that reported earlier [15].

**Figure 2 Isolated inferior vermian hypoplasia in a fetus at 20 weeks of gestation**



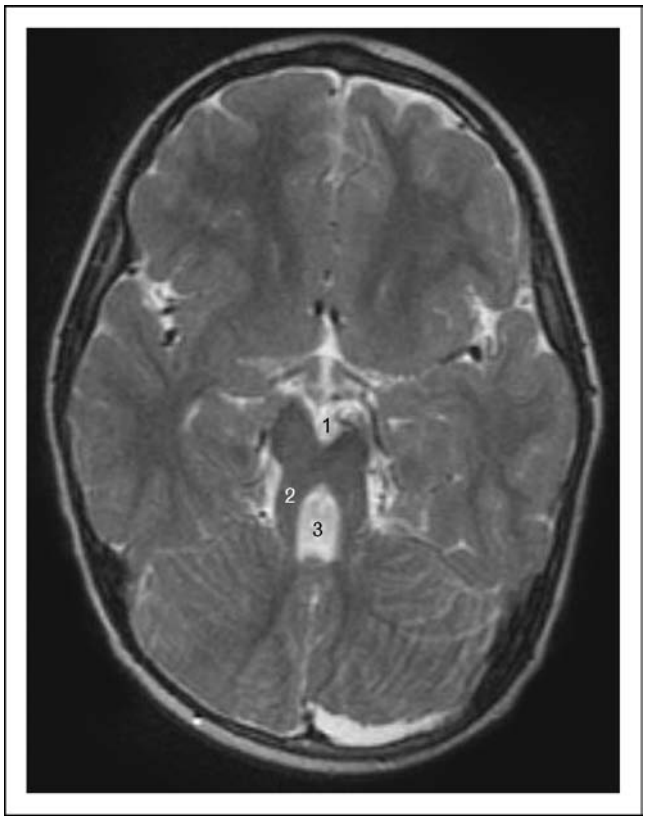
T2-weighted magnetic resonance imaging scan of the midline sagittal view. Incomplete downgrowth of vermis is indicated by the arrow.

## Conditions in which combined disturbances in cerebellar and brainstem development are prominent

Development of the cerebellum and brainstem are intimately connected. For example, the rhombic lips generate cells that lead to formation of the external granular layer of the cerebellum as well as cells to the pontine and precerebellar nuclei, such as the inferior olive. It is therefore not surprising that malformations of the cerebellum and brainstem often occur together. Joubert syndrome is an autosomal recessive condition that presents with hypotonia, disturbances in respiratory (hyperventilation and central apnea) and oculomotor control, and later psychomotor disturbances. The essential brain morphology of Joubert syndrome includes vermian hypoplasia, impaired axonal decussation (with a deep interpeduncular notch), and thick abnormally oriented superior cerebellar peduncles. Together these features give the neuroradiologic picture known as the molar tooth sign (see Fig. 3) [16]. Previously thought to be pathognomonic for Joubert syndrome, the molar tooth sign is now recognized in at least eight other conditions, known as Joubert syndrome-related disorders [14,17••,18], often with cerebral, renal, retinal, or hepatic abnormalities. At least four genetic loci have been identified for Joubert syndrome [19••], including mutations in the *AHI1* [14,20] and *NPHP1* genes [21]. The gene product of *AHI1* (Jouberin) guides axonal decussation of the corticospinal tracts and superior cerebellar peduncles, both of which are disturbed in Joubert syndrome and Joubert syndrome-related disorders [17••].

Pontocerebellar hypoplasia (PCH) is a heterogeneous group of conditions having in common an abnormally small cerebellum and pons [22–24]. When the inferior olives are also involved, the term olivopontocerebellar hypoplasia is used. The pathogenetic mechanisms underlying these conditions remain unclear although both hypoplasia and atrophy (and their combination) have been implicated. To date, five forms of PCH have been

**Figure 3 Molar tooth sign in an infant with Joubert syndrome**




T2-weighted axial view at the level of the midbrain. 1, Deep interpeduncular cistern (due to reduced pyramidal decussation); 2, thick superior cerebellar peduncle; 3, enlarged fourth ventricle.

described, distinguished by the presence of associated clinical and pathological findings. Thus, in addition to a small cerebellum and pons, PCH-1 has anterior horn-cell degeneration with spinal muscular atrophy, while PCH-2 has prominent extrapyramidal dyskinesias and progressive microcephaly. These two original forms of PCH described by Barth [25] are distinguished from other forms of PCH by relative preservation of the vermis. PCH-3 is associated with optic atrophy, progressive microcephaly, and severe congenital hypotonia, whereas PCH-4 is distinguished by relatively preserved cerebellar foliation patterns [26]. The most recently described PCH-5 form is a severe condition with a hypocellular vermis and fetal-onset myoclonic seizure-like activity [12•].

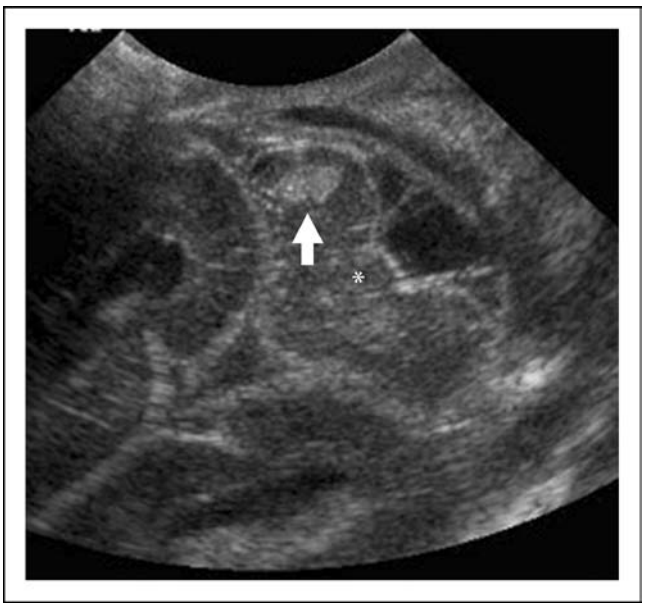
The combination of cerebellar and pontine hypoplasia suggests a rhombic-lip defect. Since the *Math1* gene is heavily expressed in the rhombic lips [27,28], and since a knockout mouse model develops neither the external granular layer nor the pontine nuclei, this gene locus has been implicated in this group of disorders. Many cases appear to have a genetic origin, with an autosomal recessive inheritance pattern. Although the precise gene loci for PCH are largely unknown, linkage studies in a recently described form of PCH (with associated progressive microcephaly, seizures, and developmental delay) have identified a genetic locus on chromosome 7q11–21 [29]. Certain inborn errors of metabolism may manifest with combined cerebellar-brainstem malformation and atrophy, including congenital disorder of glycosylation type Ia [30] and the Smith–Lemli–Opitz syndrome. However, these conditions appear distinct from the PCH types described above.

## The impact of premature extrauterine life on cerebellar growth and development

Increased survival and greater availability of sophisticated neonatal brain imaging have highlighted the risk of premature birth to cerebellar growth and development. The selective cerebellar vulnerability during the critical developmental period between 24 and 30 weeks of gestational age underlies the subsequent disrupted cerebellar development seen in ex-premature infants [31••]. The etiology is multifactorial and likely includes an interplay between programmed developmental processes, maternal and intrapartum stressors, and acute early postnatal cardiorespiratory derangements associated with premature birth.

Two forms of impaired cerebellar development can be distinguished: that occurring in infants with or without evidence during preterm life of direct cerebellar injury. Several patterns of abnormal cerebellar development have been described in ex-premature infants *diagnosed with cerebellar injury in the early neonatal period*. Very-low-birthweight infants have a particular predilection for direct cerebellar injury [31••,32••,33,34•], with up to 19% of infants born under 750 g developing ultrasound evidence of cerebellar injury in a recent study [32••]. Several reports have described an extensive and symmetric form of cerebellar injury that is invariably associated with pontine hypoplasia and supratentorial parenchymal injury [31••,33,34•]. Conversely, Limperopoulos *et al.* [32••] described a broader spectrum of cerebellar parenchymal injury (with a prominent hemorrhagic component) in preterm infants. Specifically, these lesions ranged from a milder and more prevalent form that was primarily focal and unilateral (71%), to a less common (9%) but more diffuse bihemispheric and vermian injury (see Fig. 4) [32••]. In this cohort [32••], bilateral cerebellar hemorrhagic injury ranged from partial infero-medial to near- total cerebellar destruction (similar to that previously described by Messerschmidt, Johnsen, and colleagues [31••,33,34•]). Moreover, although concomitant supratentorial lesions were common, hemorrhagic injury was confined to the cerebellum in 23% of cases [32••]. The exact pathogenesis of cerebellar injury in the preterm infant is unknown; however, several different

**Figure 4 Focal unilateral cerebellar hemorrhage in an infant at 25 weeks of gestation (arrow)**



The cranial ultrasound mastoid view is shown. The vermis is indicated by ∗.

mechanisms have been proposed. Primary cerebellar hemorrhage may result from subpial bleeding within the germinal matrix of the external granular cell layer, or the subependymal germinal matrix adjacent to the fourth ventricle (described earlier). Another proposed mechanism is vaso-occlusive injury in the inferior cerebellar artery distribution, causing extensive bilateral injury to the lower cerebellar hemispheres and the pancake-like appearance described by Johnsen *et al.* [33,34•]. Of note, Limperopoulos *et al.* [32••] and others [31••] have described a clear relationship between cerebellar lesions identified early in preterm life and subsequent impairment of unilateral or bilateral cerebellar growth and development. The potential role of undetected early-life cerebellar injury in early gestation in the pathogenesis of subsequent cerebellar hypoplasia/aplasia has been raised by several authors [24,31••,35].

Even in the *absence of direct injury* shown by neonatal MRI, the cerebellum of the premature infant appears to be at risk for impaired growth and development. Recent studies using quantitative volumetric MRI techniques have provided accumulating evidence that prematurity itself, as well as supratentorial prematurity-related injuries, may impair early postnatal cerebellar growth in preterm infants [36••,37,38•]. These quantitative MRI studies have now corroborated in the living infant earlier pathology studies showing that growth of the immature cerebellum is particularly rapid during the third trimester [39••]. In these studies [39••], the rate of cerebellar growth during the third trimester far exceeded that of the cerebral hemispheres. However, when compared with normal full-term infants, preterm infants show significantly smaller cerebellar volumes at term equivalent age, even in the absence of MRI-demonstrable cerebral or cerebellar injury. These findings raise important questions about extrauterine factors operating during the early weeks of premature life that impede cerebellar growth and development [39••]. This early-onset failure of normal cerebellar growth in ex-preterm infants appears to have an enduring effect. Allin and colleagues [40••] demonstrated reduced volumes of the cerebellar vermis and hemispheres (controlling for whole-brain volume) in ex-premature adolescents compared with their term-born peers.

The more commonly recognized forms of prematurity-related brain injury, such as germinal matrix-intraventricular hemorrhage and periventricular leukomalacia in the *cerebral* hemispheres, appear to have an adverse effect on growth of the immature cerebellum, even in the absence of direct cerebellar injury [36••,37,38•]. In fact, using advanced three-dimensional volumetric MRI and parcellation techniques, a recent study demonstrated significant crossed trophic effects of primary cerebral injury on the contralateral cerebellar hemisphere volumetric growth, and vice versa (so-called crossed cerebello-cerebral diaschisis). These effects were evident by volumetric MRI in ex-preterm infants as early as their term-equivalent age [36••]. These findings in living preterm infants provide important insights into the highly integrated anatomical and functional interactions between the cerebrum and cerebellum during third-trimester brain development.

In summary, both direct and indirect mechanisms of cerebellar injury appear to stunt cerebellar growth and development in the preterm infant. To date, cerebellar injury has been underappreciated in survivors of preterm birth. It is reasonable to suggest that early-life cerebellar growth impairment, related to either direct cerebellar injury or cerebellar underdevelopment secondary to cerebral injury, plays a previously under-recognized role in the long-term cognitive, behavioral, and motor deficits associated with brain injury among premature infants. Comprehensive long-term follow-up studies combined with quantitative brain imaging will be required to adequately address these questions.

## Conclusion

It is anticipated that greater order and consistency in our understanding of posterior fossa dysgenesis will emerge in the wake of advances in two major areas, namely fetal MRI and genetics. Fetal and neonatal MRI have enhanced the detection of increasingly small and more

subtle cerebellar structural anomalies. Since fetal detection of posterior fossa anomalies has been associated with a termination rate of up to 80% [41•], rigorous outcome studies are urgently needed to delineate the long-term clinical significance of particularly the more subtle anomalies now detected. Fetal MRI is also likely to advance our understanding of cerebellar disruptions, by identifying early acquired lesions and their impact on subsequent development. The development of quantitative MRI in the fetus, currently technically challenging, will also be a major advance, particularly for defining the genotype–phenotype relationships of these lesions.

## Acknowledgements

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## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 681).


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