a popular attending physician in the outpatient department and newborn nurseries. He also was an Oral Examiner on the American Board of Pediatrics from 1970 to 1996.

The task of following Dr Garfunkel and maintaining an outstanding pediatric forum was formidable and daunting, especially in an era of burgeoning scientific knowledge and rapidly changing clinical practice. In large part, his influence guided my editorial philosophy: To reassure authors and readers that, although Dr Garfunkel's style would be impossible to replicate, we would do all in our power to maintain the tradition of excellence established by him and his predecessors.[2] Our goal continues to be to build on the firm reputation that Dr Garfunkel established as a comprehensive publication regarding children's health issues. Another shared lesson transferred to me from Joe is to ensure diversity in the Editorial Board, with a focus on young "rising stars." This philosophy served both of us well. Dr Garfunkel's dedication to *The Journal* continued long after his retirement. As the new Editor, I would regularly receive pages torn from an issue, with handwritten comments in the margin, from the master "Editor's Editor." ■

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Postnatal Steroids in the Preterm Infant—the Good, the Ugly, and the Unknown

The neonatal team review the ventilator settings for a 25-week gestation infant weighing 780 g now aged 12 days on mean airway pressure of 10 (peak inspiration 15, peak expiratory 5, rate 40) and an oxygen requirement of 35% (respiratory index 3.5, Parikh et al[1]) and no other major complications. The neonatal fellow asks "Would postnatal steroids assist this infant to get off the ventilator or will that have the risk of significant neurological consequences?" The article by Parikh et al[1] in this issue of *The Journal* attempts to address this subject with the report of a pilot randomized trial of hydrocortisone (total dose 17 mg/kg over 7 days) in 64 extremely low birth weight infants (mean gestational age 25 weeks) with ventilator dependence after 10 days of life. The authors report that hydrocortisone administration for ventilator dependence was associated with no alteration in the volumes of brain tissue compared with placebo (the Good); no impact on respiratory outcomes with no reduction in bronchopulmonary dysplasia (BPD) or death (the Ugly). They propose that future trials of hydrocortisone should optimize the dose and population to be studied to determine efficacy and safety (the Unknown). The authors note several limitations in their study, including the dose of hydrocortisone, the outcomes of brain volumetry as a surrogate for neurodevelopmental outcome, and the concern over poor growth with both infant groups weighing 1.8 kg at term equivalent, suggesting potential confounding by neonatal malnutrition. The authors do not note that the placebo group had a combination of factors that may have led to a reduction in brain volume due to a high rate of fetal growth restriction (30% vs 19%) and brain injury with intraventriuclar hemorrhage and white matter injury (39% vs 29%, grades not specified). In addition, although contamination of physician-prescribed steroids is inevitable, it would appear that 5-6/32 in each group received additional dexamethasone and/or hydrocortisone doses. Thus, despite the important information contained within this article, gaps in knowledge of who which infants and how to apply corticosteroids in the preterm infant with ventilator dependence persist.

See related article, p 685

BPD	Bronchopulmonary dysplasia

The Good—Hydrocortisone Appears Safe for the Immature Brain

There is a body of observational data, now supported by the pilot randomized controlled trial by Parikh et al[1] in *The Journal*, that hydrocortisone appears to have no or limited adverse neurological consequences concerning brain volume in the preterm infant. Although the dose used by Parikh et al[1] is low (total hydrocortisone dose ~14 mg/kg), the Table outlines the studies with hydrocortisone doses commencing at a higher dose of 5 mg/kg/d tapering after 7 days and resulting in cumulative doses of 50-75 mg/kg. With these higher doses of hydrocortisone, there was no or minimal impact on brain volumes and neurodevelopmental outcomes into later

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Table. Studies of the neurological impact of hydrocortisone with comparisons with dexamethasone

Author	Number studied	Age	Results/conclusions
Benders 2009[19]	Hydrocortisone = 19; control = 19	Term	No difference in cerebral tissue volume at term
Tam 2011[7]	hydrocortisone = 15; hydrocortisone/ dexamethasone = 11; dexamethasone = 7; no steriods = 100 control = 16	Term	Hydrocortisone had smaller cerebellum volume
Hitzert 2012[20]	Hydrocortisone = 21; dexamethasone = 25	3 mo	Dexamethasone at 3 mo lower MOS
Watterber*,† 2007[21]	Hydrocortisone = 126; control = 126	18-22 mo	Hydrocortisone: lower incidence Bayley MDI <70 and better awareness of object permanence
Heide-Jalving 2003[22]	Hydrocortisone = 25, dexamethasone = 23	5-7 y	Head circumference in both groups: dexamethasone more special school education than hydrocortisone/control
Lodygensky 2005[23]	Hydrocortisone = 23: control = 35	8 y	No difference on the WISC-R scores and brain volumes
Rademaker 2007[24]	Hydrocortisone = 18: control = 19	8 y	No differences in magnetic resonance spectroscopy, 15-word memory test and IQ
Karemaker 2006[25]	Hydrocortisone = 52: dexamethasone = 46	7-10 y	Dexamethasone: worse cognitive, motor, and behavior outcomes.
Rademaker 2006[26]	Hydrocortisone = 99 control = 101	8 y	No difference in IQ, Visual Motor Integration test, motor function, cerebral palsy, and memory test
Ter Wolbeek 2012[27]	Hydrocortisone = 67 Dexamethasone = 63	14-17 y	Dexamethasone: adverse effects on motor function, school level, and neuropsychological functions

IQ, intelligence quotient; *MDI*, mental developmental index; *MOS*, motor optimality score; WISC-R, *Wechsler intelligence scale for children-revised.*
*Lower dose hydrocortisone 1 mg/kg/d tapering over 15 d.
†Randomized controlled trial.

childhood. In contrast, high dose dexamethasone[2] has adverse effects of brain volumes and neurodevelopmental outcomes used alone[3-6] or in comparison with hydrocortisone (Table). Within the studies of hydrocortisone, only 1 study by Tam et al[7] demonstrated an adverse neurological impact on cerebellar volumes. However, the overlap between hydrocortisone and dexamethasone in the analysis of their infants was significant, since 11/26 hydrocortisone infants also received dexamethasone, and no dose-dependent relationship between hydrocortisone dose and volume was found, raising concerns as to whether hydrocortisone had an independent effect. Further, three infants in the hydrocortisone group had evidence of cerebellar hemorrhage.

Hydrocortisone appears to have less neurological impact than dexamethasone, even with adjustment for dose equivalency. A lower dose of dexamethasone beginning at 0.15 mg/kg/d with a total dose of 0.9 mg/kg (equivalent to a total hydrocortisone dose of 22 mg/kg)[7] was associated with reductions in brain volumes at term (personal communication). There are biological differences between these agents that may be of neurological relevance. Hydrocortisone differs from dexamethasone as it possesses both mineralo- and gluco-corticoid actions. In animal models, dexamethasone, which binds only to glucocorticoid receptors, induced neuronal degeneration within the hippocampus.[9,10] In humans, alterations in hippocampal volume[11] and synaptic plasticity and associative memory[12] were reported with dexamethasone in preterm infants. It is also hypothesized that the longer biological half-life of dexamethasone relative to hydrocortisone influences potency and potential adverse effects.[13]

The Ugly—Low Dose Hydrocortisone Has Limited Efficacy for BPD

A recent meta-analysis of the impact of postnatal hydrocortisone for preventing or treating BPD reviewed 8 randomized controlled trials with a total of 880 participants.[14] There was no reduction in BPD or death with hydrocortisone. All trials started in the first week of life and utilized low dose 1 mg/kg/d for 5-12 days of treatment. Observational data from the The Netherlands suggests that a higher dose may be effective[15] and has formed the foundation for a new randomized trial of hydrocortisone in preterm infants, called Systemic Hydrocortisone to Prevent BPD in Preterm Infants (SToP-BPD)[16] with gestational age <30 weeks and/or birth weight <1250 g; ventilator-dependent at 7-14 days; and a respiratory index of ≥3.0 for more than 12 h/d for at least 48 hours. The study will administer a starting dose of 5 mg/kg/d (divided into 4 doses) for 7 days, followed by 3.75 mg/kg/d (in 3 doses) for 5 days, subsequently lowering the frequency by 1 dose every 5 days. This will result in a total of 22 days of hydrocortisone therapy with a total dose of 72.5 mg/kg. Finally, all recruiting centers have agreed to only use open label hydrocortisone as resue therapy. The study will randomize 400 infants in 15 sites across The Netherlands and Belgium, with 24 infants recruited as of July 2012. This hydrocortisone dose equates to cumulative dose of 3 mg/kg dexamethasone and thus is lower than early high dose dexamethasone trials but higher than the dose that was used in a recent trial (dexamethasone total 0.89 mg/kg over 10 days) that resulted in successful weaning from ventilation but no effect on rates of BPD or survival.[8]

The Unknown—Will High Dose Hydrocortisone Be Safe and Effective in Preterm Infants with Severe Respiratory Disease?

It appears that higher doses of hydrocortisone, above that of stress doses used in the current study, will be required for