48. Nickel K, Maier S, Endres D, Joos A, Maier V, van Elst LT, et al. Systematic review: overlap between eating, autism spectrum, and attention-deficit/hyperactivity disorder. Front Psychiatry 2019;10:708.
49. Engle-Stone R, Aaron GJ, Huang J, Wirth JP, Namaste SML, Williams AM, et al. Predictors of anemia in preschool children: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr 2017;106(Suppl 1):402S-15S.
50. Zablotsky B, Black LI. Prevalence of children aged 3-17 years with developmental disabilities, by urbanicity: United States, 2015-2018. Natl Health Stat Rep 2020;139:1-7.
51. Zablotsky B, Black LI, Blumberg SJ. Estimated prevalence of children with diagnosed developmental disabilities in the United States, 2014-2016. NCHS Data Brief 2017;291:1-8.
52. Drury KE, Schaeffer M, Silverberg JI. Association between atopic disease and anemia in US children. JAMA Pediatr 2016;170:29-34.

50 Years Ago in *The Journal of Pediatrics*

Phenylketonuria over the Years: A Story of Treatable Intellectual Disability

Wilson MG, Wu PY, Ware AG. Sex ratio in hyperphenylalaninemia of newborn infants. J Pediatr 1971;78:117-9.

Initially described in the 1930s, phenylketonuria (PKU) has become one of the most well-studied inborn errors of metabolism. Widespread newborn screening for PKU began in the mid-1960s and was based on the discovery that a specialized diet can prevent the severe intellectual disability associated with untreated disease. In the 50 years that have elapsed since this pivotal moment in preventative public health, there has been a tremendous transformation in how we understand and treat PKU.

In the 1970s, early newborn screening experience generated a hypothesis of sex-based differences in neonatal phenylalanine metabolism. Wilson et al presented data from California's first 5 years of newborn screening for PKU that showed that transient hyperphenylalaninemia was independent of sex. To this day, phenylalanine norms are interpreted independent of sex.

Around the same time as the work of Wilson et al was published, there was growing controversy about when to discontinue dietary therapy for PKU. It was becoming apparent that the brain continues to develop into adulthood, and phenylalanine restriction might need to extend past 6 years of age to avoid further cognitive decline.[1] Fifty years later, it is now generally accepted that PKU treatment should continue not just through childhood, but for life. Although nutritional management remains the mainstay of therapy for pediatric patients with PKU, novel approaches such as cofactor therapy with sapropterin hydrochloride and enzyme substation therapy with phenylalanine ammonium lyase are transforming PKU's therapeutic landscape.[2]

Despite these advances, there is still a great deal of work to be done. Over the coming 50 years, we can aspire to a greater understanding of the age-dependent neuropsychiatric effects of phenylalanine elevations, additional therapeutic alternatives that decrease disease burden, and perhaps a cure with genomic editing.

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References

1. Schuett VE, Gurda RF, Brown ES. Diet discontinuation policies and practices of PKU clinics in the United States. Am J Public Health 1980;70:498-503.
2. Vockley J, Andersson HC, Antshel KM, Braverman NE, Burton BK, Frazier DM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med 2014;16:188-200.