**Present Significance**

When diagnosed in the neonatal period and treated adequately, infants homozygous for mutations at the PAH locus grow up with near normal cognitive function. However, evaluation of the first generation of patients with PKU to reach adulthood reveals the need for improvement in screening, treatment, and follow-up; corresponding new guidelines have appeared. Meanwhile it has become apparent that all hyperphenylalaninemia is not classic phenylketonuria; a small fraction of patients have disorders of tetrahydrobiopterin synthesis or recycling that require additional diagnostic procedures in the screening program and specific forms of treatment for affected patients. It also has been recognized that maternal hyperphenylalaninemia puts the fetus at risk for microcephaly, impaired cognitive development, and congenital anomalies, all of which can be avoided by careful treatment, preconception and intrapartum, of the mother. The expanding circles of awareness about these “new” problems are additional legacies of the Guthrie test.

In November 1990, investigators from around the world convened in Paris, France, to discuss some of the emerging issues in PKU. Mutation analysis had become feasible, thanks to the availability and generous distribution by the Houston group of a probe hybridizing to the PAH gene. It would become apparent that many mutations had occurred at the human PAH locus, that some were prevalent and most were rare, and that they were distributed non-randomly in human populations according to political, ethnic, and geographic identity. A consortium was formed in 1991 (it now comprises 88 investigators in 28 countries), and a PAH gene mutation database was established. PAHdb (http://www.mcgill.ca/pahdb) has since become a prototype for locus-specific mutation databases, linked to the corresponding entry in the online version of McKusick’s catalogs of Mendelian Inheritance in Man (OMIM 261600). PAHdb contains records (on December 31, 1997) of more than 340 different mutations by state, accompanied by a vast array of descriptors of those mutations. PAHdb illustrates what is happening at the interface between genomics (which is producing results in the Human Genome Project), genetics (which is the study of human genetic variation), and medical genetics (where the associated diseases are addressed). Together, a remarkable legacy of concepts, data, and techniques has descended from the test developed by Guthrie and Susi, described in *Pediatrics* in 1963.

**REFERENCES**


**COMMENTARY**


Comments by Frank R. Greer, MD

**ABSTRACT OF ORIGINAL ARTICLE.** Data on the birth weights of 5,635 live-born Caucasian infants at 24 to 42 weeks’ gestation are presented. All infants were born from July 1948 to January 1961. Data from infants born at greater than 36 weeks’ gestation after 1955 are excluded because of the large number of infants. The socioeconomic stratum represented by this population is defined as medically indigent or part-pay. The median weights of Colorado babies (3230 g) were found to be lower at 40 weeks’ gestation that the national median (3340 g). Weight curves in the form of percentiles are generated from the data. These curves can be used as standards for
determining the adequacy of weight gain of individual infants which may be done either at the time of birth, or after birth in relation to extrauterine environmental factors.

COMMENTARY

The work described in this landmark publication by Lubchenco and colleagues is still used by every practitioner caring for newborn infants even today.1 For those of us who began our pediatric training after 1970, the Lubchenco growth curves, supplied in a convenient tablet form to most newborn nurseries by a US formula manufacturer, were a part of every newborn infant work-up. Most of us took these for granted and paid scant attention to the previous generation of newborn infant care providers who spoke of the days when the definition of a premature infant was any newborn with a birth weight <2500 g. This definition was recommended by both the American Academy of Pediatrics and the World Health Assembly.2,3 Today’s use of serial perinatal ultrasound dating of the fetus makes these “good old days” seem even more remote. Pediatricians attend deliveries with little suspense concerning the questions of gestational age and fetal growth. Yet it was this article that pointed out the importance of fetal growth and its potential relationship to both the immediate well-being and the long-range outcome of the newborn. It made possible a more precise definition of prematurity and the widespread adoption of the terms “small for gestational age,” “large for gestational age,” “intrauterine growth retardation,” and fetal dysmaturity. It also established the basis for screening infants with birth weights greater than the 90th percentile or less than the 10th percentile for potential medical problems.

To be sure, the Lubchenco curves (see Fig 1) were established in the mile-high city of Denver, CO, and subsequently, it was shown that these curves overestimated the number of infants greater than the 90th percentile (and underestimated those less than the 10th percentile) in cities at lower altitudes, which included most of the United States. The study also was criticized for including only a relatively indigent population. However, other growth curves quickly followed, most notably those of Babson4 and Usher.5 The Denver population included a large Hispanic population that accounted for 30% of the births, but the authors noted that there were no differences in birth weights between Hispanic and other Caucasian infants. Of note, the database excluded infants of “Negro, Oriental, and Indian” ethnicity. Finally, the growth curves did include twin deliveries, even though the authors pointed out that after 34 weeks’ gestation, twins fell from the 50% to the 15% by 42 weeks’ gestation. They also described separate curves for males and females, although the ~100 g weight difference between sexes was small enough that a combined curve for both sexes generally was adopted in the United States.

Just 2 years earlier, Joseph Warkany and colleagues6 had pointed out in a lengthy publication that intrauterine growth retardation was a syndrome of sorts, with significant effects on long-

Fig 1. The weights of liveborn Caucasian infants at gestational ages from 24 to 42 weeks are graphed as percentiles.
term outcome. According to Warkany: “The unsatisfactoriness of our knowledge in this area is due, to a great extent, to the false label attached to these children, whose records are pooled with those of the prematures. The lack of separation of the 2 types of children underweight at birth has led to a neglect of observations and recordings necessary for a better knowledge of this field.” Indeed a study in 1965 showed that there were as many term as preterm infants born weighing <2500 g in the United States, and that the majority of preterm infants were actually born with a birth weight of >2500 g. Building on these reports and the Lubchenco fetal growth curves, Battaglia and Lubchenco then proposed the well known classification system of large for gestational age, small for gestational age, and appropriate for gestational age for determining at-risk infants for various medical problems, initially focusing on increased mortality rate and hypoglycemia. Usher and Farr went on to begin the description of the physical characteristics differentiating premature and small for gestational age infants that also remain in wide use today.

After 35 years, the observations made by Lubchenco remain a keystone in the practice of neontology. This work is truly a landmark in its field.

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COMMENTARY

Comments by Jack P. Shonkoff, MD

ABSTRACT OF ORIGINAL ARTICLE. This report describes a constellation of clinical features found in 25 children with a history of an illness or accident from which they recovered, despite their parents’ anticipation of a fatal outcome. The paper proposes the hypothesis that children who are expected by their parents to die prematurely often react with a disturbance in psychosocial development that is rooted in the parent-child relationship, which the authors characterize as a vulnerable child syndrome. The essential features of the proposed syndrome include difficulty with separation, infantile behavior, bodily overconcerns, and school underachievement. The paper provides an overview of predisposing factors and determinants of the presenting symptoms, along with suggestions for both clinical management and primary prevention.

COMMENTARY
This classic paper by Green and Solnit illustrates the essence of the behavioral–developmental dimension of clinical pediatrics. Its brilliance is reflected in both its seminal creativity and its enduring salience over more than 3 decades. Its relevance for the practicing pediatrician remains vital to this day, and its message is particularly compelling in view of the challenges facing our highly dynamic health care system. Its implications for the academic community are similarly worthy of serious reflection.

The core contribution of this paper is the extent to which it provides a rich conceptual framework for the assessment and management of a cluster of “bread and butter” clinical concerns that permeate the worlds of primary and tertiary care pediatrics. The symptomatology that captured the attention of
Intrauterine Growth as Estimated From Liveborn Birth-Weight Data at 24 to 42 Weeks of Gestation, by Lula O. Lubchenco et al, Pediatrics, 1963;32:793–800

Frank R. Greer
Pediatrics 1998;102;237

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