

# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

**The National Institute of Child Health and Human Development and  
Phenylketonuria**

Duane Alexander

*Pediatrics* 2003;112;1514-1515

DOI: 10.1542/peds.112.6.S1.1514

**This information is current as of July 11, 2006**

The online version of this article, along with updated information and services, is  
located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/112/6/S1/1514>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2003 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# The National Institute of Child Health and Human Development and Phenylketonuria

Duane Alexander, MD

**ABSTRACT.** The National Institute of Child Health and Human Development (NICHD) was established shortly after the Guthrie test for screening newborn infants for phenylketonuria (PKU) was introduced. The NICHD supported the study demonstrating the long-term efficacy of screening and a low-phenylalanine diet in preventing mental retardation. With the identification of the adverse impact on fetal development of high intrauterine phenylalanine exposure from a mother with PKU, the NICHD organized and supported the study reported here, demonstrating the protective effect of phenylalanine restriction of the mother's diet during pregnancy. The study provides clear guidance for the management of pregnancy in women with PKU. *Pediatrics* 2003;112:1514–1515; *phenylketonuria, PKU, NICHD, newborn screening, mental retardation, maternal PKU.*

---

ABBREVIATIONS. PKU, phenylketonuria; NICHD, National Institute of Child Health and Human Development.

---

The histories of phenylketonuria (PKU) and of the National Institute of Child Health and Human Development (NICHD) are remarkably intertwined. It can easily be argued that the demonstration in the late 1950s that a genetic metabolic cause of severe mental retardation, PKU, could be prevented by a combination of screening newborn infants for elevated phenylalanine levels using the Guthrie test and treatment of affected infants with a phenylalanine-restricted diet created great excitement in the field of mental retardation, a field that had been starved for success. The optimistic view was that if we can succeed with PKU, then there must be other PKU-like conditions for which similar success could be achieved, if only we could do the research needed to discover them. This was one of the strongest arguments used by Dr Robert E. Cooke and Eunice Kennedy Shriver in championing establishment of a new institute at the National Institutes of Health to conduct, promote, and fund such research. These efforts culminated in the passage of legislation by Congress in October 1962 establishing the NICHD.

Among the early research activities supported by this new institute was a follow-up study of children whose PKU was diagnosed by newborn screening

and treated with a phenylalanine-restricted diet from the first weeks of life. This study showed that the intelligence and developmental courses of the treated children at age 7 were not significantly different from those of their unaffected siblings, strengthening the case for newborn screening. As a result of this research, every state soon required screening all newborns for PKU. This resulted in identification of approximately 250 children with PKU each year in the United States who, with treatment, were prevented from developing mental retardation and grew up to be normally functioning adults, rather than having severe retardation and usually being shunted off to residential institutions for care.

Although mental retardation and developmental disability research blossomed on many fronts as the funding from the new NICHD supported a wide range of activities, the excitement regarding PKU and newborn screening was soon dampened by 2 factors. First, although many disorders became identifiable by a variety of newborn screening techniques, only one—congenital hypothyroidism—was easy enough to identify economically and had a sufficiently effective treatment—thyroxine—to justify this approach so that every state mandated screening all newborns for it as was done with PKU. A scattering of other conditions—galactosemia, urea cycle disorders, and congenital adrenal hyperplasia, for example—were screened for by some state programs, but the dream of preventing many mental retardation syndromes by the PKU approach remains unrealized.

The second factor and the focus of this document was the discovery of maternal PKU. When treated girls with PKU reached adulthood, no longer consuming a phenylalanine-restricted diet, and began to marry and have children rather than not reproduce as in earlier times, it became apparent that their children were not normal. They had a variety of congenital anomalies, most significantly heart defects, but most important, nearly all had some degree of mental retardation. The high phenylalanine levels to which the developing fetus was exposed apparently were toxic and teratogenic. The stark realization quickly hit: unless some effective intervention could be developed, if each woman with PKU had an average of 2 children, then in 1 generation we would have as much mental retardation as a result of PKU as we had before the screening and treatment programs were developed.

---

From the National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland.  
Reprint requests to (D.A.) NICHD-NIH, Bldg 31, Rm 2 A03, 31 Center Dr, MSC 2425, Bethesda, MD 20892-2425; E-mail: da43w@nih.gov  
PEDIATRICS (ISSN 0031 4005). Copyright © 2003 by the American Academy of Pediatrics.

Reenter NICHD to the scene. The institute, under the leadership of Felix de la Cruz, chief of the Mental Retardation and Developmental Disabilities Branch, brought together leading experts in the field to discuss how to approach the problem. It was quickly agreed that the most promising approach was reinstitution of a phenylalanine-restricted diet to reduce fetal phenylalanine exposure during pregnancy, but there were many questions. Would it work at all? How soon did the diet need to be started? What level of control needed to be achieved? Would women be willing to tolerate the diet in the interest of having a healthy infant?

Working together, a protocol was developed, contracts were awarded, and the study began. It took longer than anyone anticipated (it is the longest-term

study that the institute has ever funded and 1 of the most expensive), but the results are now complete and demonstrate both success and the factors that enhance its likelihood. This supplement provides a comprehensive report on the various aspects of the study.

With the completion of the Maternal PKU Study, what remains is putting into practice what has been learned with enormous toil and considerable expense. It is hoped that this supplement will increase awareness of this problem among physicians and other health care providers and the availability of an effective treatment and help to ensure that all women with PKU know of their risk and how they can still have healthy children with timely intervention.

**The National Institute of Child Health and Human Development and  
Phenylketonuria**

Duane Alexander

*Pediatrics* 2003;112;1514-1515

DOI: 10.1542/peds.112.6.S1.1514

**This information is current as of July 11, 2006**

**Updated Information  
& Services**

including high-resolution figures, can be found at:  
<http://www.pediatrics.org/cgi/content/full/112/6/S1/1514>

**Subspecialty Collections**

This article, along with others on similar topics, appears in the following collection(s):  
**Genetics & Dysmorphology**  
[http://www.pediatrics.org/cgi/collection/genetics\\_and\\_dysmorphology](http://www.pediatrics.org/cgi/collection/genetics_and_dysmorphology)

**Permissions & Licensing**

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
<http://www.pediatrics.org/misc/Permissions.shtml>

**Reprints**

Information about ordering reprints can be found online:  
<http://www.pediatrics.org/misc/reprints.shtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

