COMMENTARY


Comments by Charles R. Scriver, MDCM

ABSTRACT OF ORIGINAL ARTICLE. The article describes a “microbial inhibition assay” for rapid and economical measurement of phenylalanine levels in whole blood. Capillary blood, from a heel prick, is collected from the newborn infant onto Schleicher and Schuell no. 903 filter paper; a disk of the sample is then transferred to an Agar plate containing a heavy inoculum of Bacillus subtilis ATCC 6051; an inhibitor of bacterial growth (β-2-thienylalanine) is counteracted by any significant excess of phenylalanine in the blood sample; and semiquantitative positive tests (hyperphenylalaninemia) are recorded by size of the bacterial growth zone in the Agar around the filter paper disc. The method permits mass screening for hyperphenylalaninemia.

COMMENTARY

The article I selected for the 50th anniversary supplement to Pediatrics describes a method. Its application has gone around the world, changed the natural history of a disease (phenylketonuria), and, through genetic screening, has introduced new concepts and approaches to the practice of medicine and health care.

Context

Lionel Penrose1 recognized phenylketonuria (PKU) as the first example of chemically impaired human cognitive development. He anticipated that this multifactorial disease, in which the necessary and sufficient components were recessive mutation in a gene and exposure to an essential nutrient (phenylalanine), might be treated to restore metabolic homeostasis and prevent disease. A decade later, three groups2–4 reported a successful chemical response to dietary restriction of phenylalanine in pilot studies on patients with PKU. The next obvious requirement was for a simple screening test that could be applied soon after birth, in the live birth population, before the postnatal cognitive impairment begins in the infant with PKU; a test sufficiently sensitive to detect one affected infant among 10 000 unafected. Although other methods met the requirements of a screening test,5 it was the Guthrie test that became most widely used.

The prospect of screening thousands of newborns became a fact; the particular prospect of a false-negative test result came to haunt its users. Newly recognized ethical, legal, social, and economic issues soon attached themselves to the Guthrie test and the universal newborn screening it catalyzed. The issues became a major challenge for the American health care system (a challenge both lesser and different in societies where universal health care was emerging or already existed). The National Academy of Science (USA) convened an international committee of experts and consultants to examine the issues. The corresponding report6 provided universal guidelines for “genetic screening” as it became known. Another report7 came 2 decades later from the Institute of Medicine, offering renewed guidelines for the somewhat different procedure known as genetic testing.

Both genetic screening and genetic testing are searches for persons possessing certain genotypes that 1) cause or predispose to disease; 2) may lead to disease in descendants; and 3) identify other variations of interest. A positive test result can lead to three results: 1) early diagnosis and effective treatment to prevent disease; 2) counseling about reproductive options to avoid the consequences of heredity; and 3) knowledge of the frequency and distribution of genetic variation in society. Genetic screening is an activity directed at populations; genetic testing is one directed at persons or families already known to be at elevated risk for a genetic disease. An emerging societal view of genetic disease and the relevance of genetic screening and testing to alter its effect on persons, families, and communities is one legacy of the Guthrie test.
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.7 Meanwhile it has become apparent that 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.9 It also has been recognized that maternal hyperphenylalaninemia10 puts the fetus at risk for microcephaly, impaired cognitive development, and congenital anomalies, all of which can be avoided by careful treatment, preconception and in-trapartum, 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.11 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 nonrandomly 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 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

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

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...

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