SCREENING OF NEWBORN INFANTS FOR METABOLIC DISEASE

COMMITTEE ON FETUS AND NEWBORN

AN OPPORTUNITY to establish screening procedures for case-finding in a number of metabolic diseases now exists in the United States, because most infants are born in hospitals where appropriate screening can easily be carried out. Case-finding in the neonatal period facilitates early inauguration of therapy, genetic counseling, and improved understanding of the natural history and incidence of metabolic diseases.

The Committee on Fetus and Newborn considered four types of screening programs: (1) screening of all newborn infants, (2) screening of specific groups of neonates with increased risk of certain disorders, (3) large scale, pilot-screening programs, designed primarily for research and acquisition of knowledge about the natural history of disease, (4) screening of expectant mothers, particularly using tests of amniotic fluid.

The committee did not consider screening of older children. However, it is emphasized that a number of important diseases, e.g., Wilson's disease, cannot be detected by screening in the first few days of life.

In evaluating screening tests for specific diseases, the Committee based its recommendations on the following criteria:

1. Does the seriousness of the disorder justify screening?
2. Is therapy for the disease in question available?
3. Is there a clearly identifiable segment of the population with an increased incidence of this disease?
4. Is it possible to perform reliable screening during the first few days of life?
5. Can the screening test be performed in a routine service laboratory?
6. Is the test acceptable to the physician and to a majority of parents?
7. Is the cost of the test acceptable?
8. Are there acceptable medical facilities prepared to confirm diagnosis and consult about the institution of therapy?

RECOMMENDATIONS

At the present time the Committee believes the following recommendations on screening programs are justified:

Phenylketonuria

A blood test for elevated concentration of phenylalanine performed no sooner than 24 hours after onset of milk feeding and prior to discharge is recommended for all newborn infants.*

A second blood test at 4 or 6 weeks of age is recommended for all infants. This will detect infants who had borderline or low plasma concentrations of phenylalanine in the first few days of life. It will also confirm a positive initial test.

Particular attention should be given to newborn infants in families in which another member is already known to have phenylketonuria, with these infants tested daily during the hospital stay. If results are negative at discharge, the infant should be tested at 1, 2, and 6 weeks of age.

Because of the difficulty of interpreting blood tests and the hazard of unwarranted dietary restrictions, it is recommended that the screening tests be performed in a large

* Particular care must be exercised in interpreting results of tests in low birth-weight infants for the accumulation of phenylalanine and the urinary excretion of reducing substances because positive findings may not indicate an inherited metabolic disorder in this group of neonates.

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central facility, such as a state health department, or at least regional laboratory. Only a very large facility will experience a sufficiently large number of tests positive for this rare disorder to acquire skill in diagnosis.

It is also most important that the laboratory have a close working relationship with a medical center where the diagnosis can be confirmed, the treatment diet chemically monitored, and the therapy supervised.

**Mellituria**

Every newborn should have a test for reducing substances (i.e., not utilizing glucose oxidase) in the urine on the day of discharge from the hospital.

The test should be carried out by the individual hospital laboratory.

It should be noted that metabolic disorders involving galactose and fructose (e.g., hereditary fructose intolerance) will not be detected in infants who have not been exposed to the substance in their diet, e.g., fructose excretion will appear only if sucrose or fructose were present in the feeding of an infant with fructose intolerance.

For newborn siblings in families of known galactosemics the following test is recommended: heparinized cord blood should be obtained for measurement of galactose-1-phosphate uridyl transferase activity. The infant should be placed on a lactose-free milk substitute until galactosemia can be ruled out. If cord blood cannot be examined, a heparinized specimen of blood should be obtained as soon after birth as possible.

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* See footnote on page 499.

† If local facilities are not available, information concerning this determination may be obtained by phoning one of the following institutions: Children's Hospital of Los Angeles, Los Angeles, California (Dr. George N. Donnell); The Children's Hospital Research Foundation, Cincinnati, Ohio (Mrs. Helen K. Berry); Babies Hospital, New York, N.Y. (Dr. Ruth C. Harris).

**Other Metabolic Diseases**

After considering a number of other possible screening programs for diseases including maple syrup urine disease, fibrocystic disease, succinylcholinesterase deficiency, glucose 6-phosphatase dehydrogenase deficiency, cretinism, and gargoylism, the Committee believes that at the present time screening tests for these disorders are not ready for application to all newborns. All infants born into a family in which an inherited metabolic disorder has been recognized previously should be carefully evaluated in the neonatal period and appropriate screening tests should be performed wherever possible.

The Committee urges that large-scale, research-oriented screening programs be undertaken at several centers; that several methods, including multiple inhibition assay, the newer chromatographic techniques developed for screening purposes, etc., be used in parallel, on blood samples; that all infants studied in the immediate neonatal period be studied again at 4-6 weeks. In this way, incidence and natural history of a large number of inheritable metabolic diseases may be investigated. In addition, the most appropriate and efficient screening techniques can be determined. As knowledge accumulates such tests might become applicable to all newborns or older infants on a routine basis.

There is insufficient evidence at the present time to warrant screening of all expectant mothers.

**Committee on Fetus and Newborn**

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IN RESPONSE to many requests from individuals and agencies, the following statement on the present status of treatment of phenylketonuria (PKU) has been prepared. The Committee on Fetus and Newborn has reviewed the present status of neonatal screening for inborn errors of metabolism (e.g., PKU and related problems) and is reporting separately.

There is considerable discrepancy of opinion regarding the treatment of phenylketonuria. The enthusiasts say that with adequate mass screening, diagnosis, and early treatment, phenylketonuria can be eliminated as a cause of mental retardation; the doubters believe that there is need to improve screening procedures and that the efficacy of treatment leaves much to be desired.

AREAS OF AGREEMENT ON TREATMENT

In spite of discrepancies in the available data, certain facts appear to warrant acceptance, namely:

1. If PKU is detected early, and the infant is started on the proper diet before 6 months of age, and then is "adequately" maintained, the child usually will demonstrate borderline to average intelligence at 5 years of age. The earlier treatment is begun, in general, the better the result.

2. For the infant being treated with a diet low in phenylalanine, the acceptable concentration of phenylalanine in the serum probably lies above 3 mg/100 ml and below 8 mg/100 ml. Some insist that it be kept below 4-6 mg/100 ml. Concentrations over 12 mg/100 ml are almost certainly too high to achieve best results.

3. For optimum results the diet must be maintained rigidly and constantly, and at the same time the parents must also offer the child the usual affection, stimulation, discipline, and security necessary for normal behavioral development.

4. Wide individual variations exist in the dietary intake of phenylalanine (20-40 mg/lb in the newborn, and 8-20 mg/lb in the older child) which will result in acceptable levels of phenylalanine in the serum.

5. Frequent accurate determinations of the concentration of phenylalanine in the serum appears to be an integral part of management in order to maintain phenylalanine at a level which will permit normal physical growth without interfering with the development and function of the brain. Such determinations may be needed daily at the onset, then weekly or monthly, depending on the parents' ability to carry out prescribed dietary therapy.

Because of these and other problems of diagnosis and management, most clinics attempting optimal service to children with PKU utilize a multidisciplinary team. The co-ordination of pediatric, social work, psychological, nutritional, and nursing skills in such a team, together with the assistance of a qualified biochemical laboratory, facilitates good care of these children as well as studies of possible improvements in diagnosis and treatment. Since many pediatricians complete their training without ever seeing a case, and/or without the oppor-
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