

Minnesota Attorney General: Administrative Rules Proceedings

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Version 3
August 20, 2018

Our File: 506

Terry P. O'Brien
Special Assistant
Attorney General

May 21, 1979

Joanne E. Hinderaker

In the Matter of the Proposed Amendments to 7 MCAR § 1.172 Relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

#506 Dept of Health

RULES REVIEW CHECKLIST

DATE RULES RECEIVED 2/9 Temporary Rule _____

Resubmitted and Received 5/15/79

DUE DATE 3/1

a. Returned to Agency w/o filing w/Secy of State 3/1/79
b. Approved 5/18/79 Date Sent Back to Agency 5/21-79

- -

1. Rules as Adopted ✓
2. Rules as Proposed ✓
3. Certificate of Board's Authorizing Resolution, where applicable n/a
4. Order for Hearing ✓
5. Notice of Hearing ✓
   (i) Sufficiency ✓
6. Secretary of State's List ✓
7. Certificate of Acquisition of Secretary of State's List ✓
8. Affidavit of Mailing ✓
   (i) At least 30 days prior to hearing ✓

no copies to file but the originals were O.K.

9. Statement of Need and Evidence ✓
10. Hearing Examiner's Report ✓
11. Agency's Findings of Fact ✓
12. Certificate of Board's Resolution Adopting Rules, where applicable n/a
13. Order Adopting ✓
14. Report of Chief Hearing Examiner ✓
    (i) Finding of No Substantial Change ✓
    (ii) Permission to Incorporate by Reference, where applicable n/a
15. Certificate of Compliance with Rulemaking Procedures ✓
16. Copy of Notice of Intent to Solicit Outside Opinion, where applicable n/a
17. Petition by Public, where applicable n/a.

Rules as Finally Adopted
10 Apr 79

DEPARTMENT OF HEALTH

RULES RELATING TO TESTS OF INFANTS FOR INBORN METABOLIC ERRORS CAUSING MENTAL RETARDATION

Chapter Eleven: 7 MCAR § 1.172

The Rules published at State Register, Volume 3, Number 13, pp. 679-682, October 2, 1978 (3 S.R. 679) as proposed, are adopted with the following amendments:

A. PURPOSE AND SCOPE OF THE RULE

This Rule describes the responsibilities of the hospitals, physicians and the Minnesota Department of Health to assure that all newborn infants are screened for phenylketonuria, galactosemia and hypothyroidism.

B. DEFINITIONS

For the purposes of this Rule, the following terms have the meanings given them:

1. "Attending physician" means the physician who is identified on the specimen card as the physician submitting the specimen.
2. "Newborn infant" means a child from birth through the first five days of life.
3. "Positive screening results" means that laboratory tests clearly indicate that the child has a high risk for developing one or more of the diseases covered by this Rule.
4. "Responsible party" means the administrative officer or other person in charge of each hospital where the child is born, and the ~~person required to register the birth of a child (Minnesota Statute § 144.159, 1976*).~~ physician or other person operating under the supervision of a physician in attendance at the birth, or if not so attended, one of the parents.

~~* The physician, midwife, or other legally authorized person in attendance at the birth, or if not attended, one of the parents, shall within 5 days subscribe and file a certificate of birth on a form prescribed by the Commissioner of Health for that purpose, with the local registrar of the district within which the birth occurred."~~

5. "Screen" means to carry out a series of laboratory tests on a dried capillary blood specimen which will identify those newborn infants who may develop phenylketonuria, galactosemia and/or hypothyroidism.

6. "Specimen" means a specimen of dried capillary blood from the newborn infant collected on a specimen card.

7. "Specimen card" means a filter paper card provided by the Minnesota Department of Health and used to collect the specimen.

C. RESPONSIBILITIES OF PARTIES INVOLVED IN THE NEWBORN METABOLIC SCREENING PROGRAM

1. The responsible party shall do all of the following:

(a) Inform the parent(s) or legal guardian that their newborn(s) will be screened for the metabolic diseases phenylketonuria, galactosemia and hypothyroidism, and explain the reasons for such screening and their right to refuse this screening on the grounds that such tests conflict with their religious tenets and practices.

(b) Collect or have collected a specimen for screening no later than the fifth day after the infant's birth, unless the parents lawfully object to such screening. If this specimen is taken prior to the third day of life or prior to 24 hours after beginning breast or milk formula feeding, the responsible party shall notify the parents or legal guardian verbally and in writing of the necessity of having the PKU test repeated on their newborn not later than the 14th day of life. If taking a blood sample at the times specified above is medically contraindicated, the sample shall be taken as soon as the infant's condition permits.

(c) Record on a permanent record the date the specimen is collected.

(d) Send the specimen and the following information to the Minnesota Department of Health laboratory within 24 hours after collection:

(1) Newborn Infant's Name

(2) Sex

(3) Mother's Name

(4) Home Address

(5) Date of Birth

(6) Date of First Feeding

(7) Date Specimen Collected

(8) Name and Address of Attending Physician and Hospital Submitting Specimen

(9) County

(10) Premature (Yes or No)

(11) Bottle Breast Both

(e) If the newborn infant is transferred to a second health care facility before the specimen is collected, the responsible party shall inform the second facility of this fact and may delegate to it the responsibility for collecting and transmitting the specimen.

2. The Minnesota Department of Health shall do all of the following:

(a) Develop specimen cards and make them available at no charge to the responsible party.

(b) Maintain a record of all cases of phenylketonuria, galactosemia and hypothyroidism reported to it.

(c) Notify the attending physician within 24 hours, verbally or and in writing by deposition in first class mail, of positive screening results and provide consultation on diagnostic and treatment sources available.

3. The attending physician shall do all of the following:

(a) Report, in writing, all confirmed diagnoses of phenylketonuria, galactosemia, and hypothyroidism to:

Human Genetics Unit

Minnesota Department of Health

717 S.E. Delaware Street

Minneapolis, MN 55440

(b) If he refers a patient with positive screening results to a medical specialist for diagnosis and/or treatment, he may delegate the responsibility for reporting a confirmed diagnosis to the medical specialist.

APPROVED AS TO FORM AND LEGALITY

MAY 18 1979 19

WARREN SPANNAUS, ATTORNEY GENERAL

BY Joanne Hinderaker
SPECIAL ASSISTANT ATTORNEY GENERAL

STATE OF MINNESOTA
DEPARTMENT OF STATE
FILED
MAY 18 1979
Joan Anderson Growe
Secretary of State
2:00 PM

Mar '79

ADMIN 1000 (Rev. 1/78)

STATE OF MINNESOTA

DEPARTMENT Attorney General

Office Memorandum

TO : Joanne Hinderaker
Special Assistant
Attorney General

DATE: May 15, 1979

FROM : Terry P. O'Brien
Special Assistant
Attorney General

PHONE: 6-5371

SUBJECT: In the Matter of the Proposed Amendments to 7 MCAR § 1.172 Relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

Enclosed for your review and filing are documents in support of the above-referenced rules. Please note that subsequent to your memo of March 1, 1979, the Commissioner of Health issued an amended order adopting rules on April 10, 1979, and the Chief Hearing Examiner issued a report on April 24, 1979, concluding that the changes made to the rules as required by the Attorney General were not substantial changes.

I believe the amended order adopting the rules specifically addresses the concerns of your memo.

If you have any questions, please do not hesitate to contact me. Thank you.

TPO:rlb

Enclosure

RECEIVED
MAY 15 1979
ATTORNEY GENERAL
ADMINISTRATIVE AGENCIES

HLTH-79-007-HC

STATE OF MINNESOTA
OFFICE OF HEARING EXAMINERS

FOR THE DEPARTMENT OF HEALTH

IN THE MATTER OF THE PROPOSED)
AMENDMENTS TO 7 MCAR § 1.172)
RELATING TO TESTS OF INFANTS)
FOR INBORN METABOLIC ERRORS)
CAUSING MENTAL RETARDATION.)

REPORT OF THE
CHIEF HEARING EXAMINER

The above-entitled matter was previously submitted to the Chief Hearing Examiner for review. On January 23, 1979, the Chief Hearing Examiner issued his report. Subsequently, after filing with the Attorney General, the Attorney General rejected the rules on March 1, 1979, requiring certain changes be made. By order dated April 10, 1979, the Commissioner of the Minnesota Department of Health again adopted the rules making changes as required by the Attorney General.

The rules were re-referred to the Chief Hearing Examiner for a second review.

Upon review, the Chief Hearing Examiner finds that the changes made to the rules as required by the Attorney General are not substantial changes requiring either withdrawal or rehearing.

Now, therefore, upon receipt of this Report, the Department of Health has the responsibility of submitting the complete hearing record and the rules as adopted by the Department to the Attorney General, notifying all persons who requested to be informed that the hearing record has been submitted to the Attorney General, and publishing in the State Register, all pursuant to Minn. Stat. § 15.0412, Subd. 4.

Dated this 24th day
of April, 1979.

DUANE R. HARVES
Chief Hearing Examiner

STATE OF MINNESOTA

COUNTY OF HENNEPIN

BEFORE THE MINNESOTA

COMMISSIONER OF HEALTH

In the Matter of Proposed Amendments to 7 MCAR § 1.172 Relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

AMENDED ORDER ADOPTING RULES

The Findings of Fact, Conclusions and Order issued on January 19, 1979, which adopted the above-referenced rules, are confirmed and continued except as such order may be inconsistent with this Amended Order Adopting Rules. The rules approved in the Findings of Fact, Conclusions and Order issued on January 19, 1979, shall be adopted except that such rules shall be modified in accordance with the changes as recommended by the Office of the Attorney General. These changes as set forth herein are as follows:

1. 7 MCAR § 1.172B.4. originally defined "responsible party" to include, ". . . the person required to register the birth of a child (Minn. Stat. § 144.159, 1976*)." The asterisk footnoted a quote from the referenced statute. Inasmuch as Minn. Stat. § 144.159 was repealed by Minn. Laws 1978 ch. 699 § 17, reference to the statute and the footnote quote of the statute are deleted from the rule as finally adopted. The rule as finally adopted shall read as follows:

> 4. "Responsible party" means the administrative officer or other person in charge of each hospital where the child is born, and the physician or other person operating under the supervision of a physician in attendance at the birth, or if not so attended, one of the parents.

2. 7 MCAR § 1.172C.2.(c) requires the Department to notify the attending physician of positive screening results within 24 hours verbally "or" in writing. Inasmuch as there

was a typographical error in the rule as submitted to the Attorney General, the conjunction "or" is to be deleted in the rule as finally adopted, and the conjunction "and" shall be substituted in its place. The rule as finally adopted shall read as follows:

> (c) Notify the attending physician within 24 hours, verbally and in writing by deposition in first class mail, of positive screening results and provide consultation on diagnostic and treatment sources available.

Dated: April 10, 1979

STATE OF MINNESOTA

COMMISSIONER OF HEALTH

George R. Petterson M.D.

GEORGE R. PETTERSEN, M.D.
Commissioner

STATE OF MINNESOTA
OFFICE OF HEARING EXAMINERS

FOR THE DEPARTMENT OF HEALTH

In the Matter of Proposed Amendments to 7 MCAR Sec. 1.172 Relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation.

REPORT OF HEARING EXAMINER

The above-entitled matter came on for hearing before Harry Seymour Crump, Hearing Examiner from the State Office of Hearing Examiners on November 6, 1978, in the Board Room of the Minnesota Department of Health Building, 717 Delaware Street, Southeast in the City of Minneapolis, County of Hennepin, State of Minnesota.

This Report is a part of a rule hearing procedure pursuant to Minn. Stat. Sec. 15.0411 to Sec. 15.047 and Sec. 15.052, to determine whether the proposed rules should be adopted and given the force of law. A copy of this Report may be obtained from the Office of Hearing Examiners for the cost of reproduction.

Members of the Department of Health (hereinafter "the Department") panel appearing at the hearing included the following: Lee E. Schacht, Ph.D., Supervisor, Human Genetics Unit; Malcolm B. Jenkins, Ph.D., Geneticist; Dwayne Morse, Dr., Ph.D., Director, Medical Laboratories; Ronald G. Campbell, M.D., Chief, Section of Maternal and Child Health; Richard P. Nelson, M.D., Chief, Section of Crippled Childrens Services; and Terry O'Brien, Special Assistant Attorney General assigned to the Department.

Eighteen public witnesses appeared and four spoke at the hearing. The Department submitted 13 written exhibits, including two prehearing public comments. Nine written post-hearing comments, including one from the Department, were received prior to the closing of the record five working days following the hearing.

Pursuant to Minn. Stat. Sec. 15.0412, subd. 4, this Report shall be available for review to all affected individuals upon request for at least five days.

The Department shall, if it proposes to adopt the rules as originally proposed or amended, submit the complete hearing record, including its Findings and Order, to the Chief Hearing Examiner no earlier than five days subsequent to the receipt of this Report. This submission shall clearly indicate any changes made to the rules as originally proposed, preferably in the format that will be submitted to the State Register for publication. The Chief Hearing Examiner shall complete his review and submit his report to the Department on the issues of substantial changes in the rule and compliance with Minn. Stat. Sec. 15.0412 within ten calendar days. Thereafter, the Department shall be responsible for filing the rules with the Attorney General and for notifying persons who have indicated that they wish to be notified of such filing.

Based upon all the records and proceedings herein, the Examiner makes the following:

FINDINGS OF FACT

1. On September 15, 1978, the Department filed the following documents with the Chief Hearing Examiner:

(a) A copy of the proposed rules.
(b) The Order for Hearing proposed to be issued.
(c) The Notice of Hearing proposed to be issued.
(c) A Statement of the number of persons expected to attend the hearing and estimated length of the Agency's presentation.

2. On October 2, 1978, a Notice of Hearing and a copy of the proposed rules were published at 3 State Register 679.

3. On September 27, 1978, the Department mailed the Notice of Hearing to all persons and associations who had registered their names with the Secretary of State for the purpose of receiving such notice.

4. On October 11, 1978, the Department filed the following documents:

(a) The Order for Hearing.
(b) The Notice of Hearing as mailed.
(c) The Affidavit of Receipt of the Secretary of State's list.
(d) The Affidavit of Mailing the Notice to all persons on the Secretary of State's list.
(e) The Secretary of State's list.
(f) The Statement of Need and Reasonableness.
(g) All materials received following a Notice of Intent to Solicit Outside Opinion published at 2 State Register 1224 (December 19, 1977). No materials were received by the Department from the public with respect to this provision.
(h) The names of Department personnel who will represent the Agency at the hearing together with the names of any other witnesses solicited by the Agency to appear on its behalf.

The documents were available for inspection at the Office of Hearing Examiners from the date of filing to the date of the hearing.

5. The record remained open through November 14, 1978, for the receipt of written comments and statements.

6. The Department cites Minn. Stat. Sec. 144.125 (1976) as its statutory authority for the promulgation of proposed rule 7 MCAR Sec. 1.172. This statute authorizes, in accordance with rules prescribed by the Department, the manner of testing, recording and reporting the results of tests regarding inborn errors in metabolism causing mental retardation.

Minn. Stat. Sec. 144.05 provides as follows:

> The authority shall include but not be limited to the following:
>
> (a) Conducts studies and investigations, collect and analyze health and vital data, and identify and prescribe health problems;
>
> (b) Plan, facilitate, coordinate, provide, and support the organization of services for the prevention and control of illness and disease and the limitation of disabilities resulting therefrom;
>
> (c) Establish and enforce health standards for the protection and promotion of the public's health such as quality of health services, reporting of disease, regulation of health facilities, environmental health hazards and manpower; . . . .

Minn. Stat. Sec. 144.112 (1976) authorizes the Commissioner of Health to promulgate regulations (rules) for the preservation of public health. Minn. Stat. Sec. 144.06 (1976) authorizes the Commissioner of Health to provide instruction and advice to mothers and their infants after birth.

7. The purpose of the proposed rule 7 MCAR Sec. 1.172 is to expand the screening of newborn infants to include galactosemia and hypothyroidism. Existing rule 7 MCAR Sec. 1.172 provided for the testing for phenylketonuria (hereinafter "PKU") since a cost effective method of screening tests for PKU existed. Due to advances in science and the art of screening procedures, it is now technically possible and economically cost effective to screen for galactosemia and hypothyroidism as well as PKU. The proposed rule provides for the screen testing of these conditions with the same specimen in order to facilitate prompt diagnosis and to ensure prompt treatment of children with these conditions.

7 MCAR Sec. 1.172

8. Existing rule 7 MCAR Sec. 1.172 (a), (b), (c), (d) and (e) deal with screening (testing) of newborn infants for PKU. This entire rule was deleted and drew no specific comments. The deletion of this existing rule is reasonable and needed to update the screening procedure for PKU and to expand the scope of screening to include galactosemia and hypothyroidism.

9. Proposed rule 7 MCAR Sec. 1.172 A. and B. set forth the purpose and scope of the proposed rule and the definitions of seven terms mentioned in the rule. These sections drew no comment and are reasonable and needed. The Department's Statement of Justification relating to these sections are hereby adopted as findings.

10. Proposed rule 7 MCAR Sec. 1.172 B.4. defines "responsible parties". The proposed rule appears to reference Minn. Stat. Sec. 144.159 (1976) which specifies those persons responsible for the filing of a birth certificate. In addition, this provision in the form of a footnote quotes that portion of the statute. However, the footnote does not constitute an affirmative rule as presented. The proposed rule places the burden on the "responsible party" to comply with this rule. A person who falls within the statutory definition of persons required to file birth certificates may not know whether she or he is required to comply with these rules unless the statutory definition is provided. The duplication of the language of Minn. Stat. Sec. 144.159 is crucial to those affected by the proposed rule. The Department, however, may in the alternative reference the applicable statute in the proposed rule as a part thereof.

11. Proposed rule 7 MCAR Sec. 1.172 C. deals with the responsibilities of parties involved in the newborn metabolic screening program. Section 1.172 C.1.(a) requires the responsible party to explain to the parents or legal guardian of the newborn the reasons for the intended screening and their right to refuse this screening. This explanation is most easily provided within a few days of the birth under the direction of the responsible party. Several public witnesses suggested that a brochure be developed to inform the parents and to simplify the consent process. The Department, in

its post-hearing comments, opposed including this suggestion in the proposed rules. This rule is needed and reasonable.

12. Proposed rule 7 MCAR Sec. 1.172 C.1.(b) requires that the specimen for screening be collected no later than five days after the birth of the infant. If the specimen is taken too soon after birth or before institution of milk feeding, the level of blood phenylalanine may not rise enough to be detected by screening. Accordingly, a second specimen needs to be obtained. The rule places the responsibility for obtaining a second specimen with the parents. This information is supplied to the parents or guardian in writing by the responsible party. At the hearing, John F. Hick, M.D., Mayo Clinic, expressed concern that the screening of breast-feeding infants may not detect PKU because the breast may not initially provide enough dietary protein to elevate the blood phenylalanine level which results in positive test results. The Department disagreed with Dr. Hick's concern. It commented that the minimum time in the proposed rule is three days after birth, or 24 hours after breast-feeding which is, in the Department's opinion, sufficient to provide adequate dietary protein. Further, the Department believes that in the hands of a competent centralized laboratory, a three-day minimum time is justified. See Department Exhibit 9, Sub-Exhibit A, which is adopted as Findings for Justification of this rule.

a. By post-hearing comment, Thomas O. Swallen, M.D., suggested that the term "breast-feeding" as used in Section C.1.(b) of the proposed rule is ambiguous. The Department agreed and recommended that the wording in line 5 of Section C.1.(b) be amended to read "beginning breast or milk formula feeding, the responsible party shall notify the . . .". This amendment is to clarify the rule and will not constitute a substantial change. The rule, as modified, is needed and reasonable.

b. The Department opposed another recommendation by Dr. Swallen to amend this rule to allow for the repeat PKU test to be done at the first routine office visit of the newborn infant (usually one month after birth) rather than requiring a separate earlier visit for this purpose. The Department commented that if screening test is delayed, treatment of the affected infant would also be delayed which could result in permanent damage to the infant. See Department Exhibit 9.

13. Proposed rule 7 MCAR Sec. 1.172 C.1.(c) drew no comments and is needed and reasonable.

14. Proposed rule 7 MCAR Sec. 1.172 C.1.(d) requires the specimen and certain general information on the newborn infant be sent to the Minnesota Department of Health laboratory within 24 hours after collection. Dr. Homberger, Mayo Clinic, at the hearing, submitted a written statement recommending that Section 1.172 C.1.(d) of the proposed rule be changed to allow the performance of assays by either the laboratories of the Department of Health or those laboratories that can demonstrate to the Department the competency to perform these assays. Similar opposition was stated in post-hearing comments by Robert S. Flom, M.D.; D. K. Ohrt, M.D.; and Michael B. O'Sullivan, M.D.. They also recommended that the Department develop criteria or methods for identifying those laboratories which would be qualified to carry out the newborn

metabolic screening test. The Mayo Clinic, in Public Exhibit 2, states that any laboratory which meets the accreditation requirements of the College of American Pathologists and the Center for Disease Control (CDC) should be allowed to perform these assays. The Department commented that tests referenced to by the Mayo Clinic in Public Exhibit 2 are not the same as the screening tests used by the Department; the Mayo Clinic tests described are actually diagnostic tests. In opposing any amendment to this rule, the Department commented that it is responsible for the public health of the state. The screening of newborns for metabolic diseases which cause mental retardation if undetected and treated is a basic public health problem and concern. Accordingly, the Department must assume arrangements that such screening for identification of those newborns at risk for developing any of these diseases, is done for large numbers of newborns, is inexpensive and has a high degree of accuracy in identifying the at-risk newborns. The centralized laboratory of the Department is the best method to assure such results. See the Department's Statement of Justification and its attached exhibits. The Department's position was also supported at the hearing by Robert A. Ulstrom, M.D., Professor of Endocrinology and Pediatrics at the University of Minnesota. In its post-hearing comments the Department specifically pointed out that it has no intention or statutory authority to prevent any laboratory from performing whatever assay it wishes and/or is ordered by the attending physician. These assays may supplement or duplicate those performed by the Department in keeping with the requirement of this rule. Another concern of Mayo Clinic was that the same laboratory should perform both "baseline and follow-up assays". The Department commented that it does not consider this to be a major issue in assuming the usefulness of metabolic screening test results. The Hearing Examiner concludes that this rule is needed and reasonable and complies with the requirements of Minn. Stat. Sec. 144.125.

15. Proposed rule 7 MCAR Sec. 1.172 C.1.(e) deals with identifying the responsibility for screening in instances where an infant changes primary care facility soon after birth. This rule drew no specific comments and is both reasonable and needed.

16. Proposed rule 7 MCAR Sec. 1.172 C.2. describes the role of the Minnesota Department of Health in newborn screening. By a prehearing comment and at the hearing, Dr. Hick pointed out that this rule makes no mention of MDH reporting responsibility. By post-hearing comment, the Department agreed with Dr. Hick's comments and recommended that this rule be amended as follows:

> (c) Notify the attending physician as quickly as possible, verbally and in writing, of positive screening results and provide consultation on diagnostic and treatment resources available.

The Hearing Examiner concludes that the term "as quickly as possible" is so vague as to be unreasonable and will will not sufficiently inform the responsible party of a time period in which the Department will report any positive screening tests for treatment to begin within a medically acceptable turnaround time for prevention of morbidity and treatable conditions. The Hearing Examiner recommends that a maximum time period for the Department to report

positive screening be stated in this amendment. So modified, as recommended by the Hearing Examiner, the rule will not constitute a substantial change and is needed and reasonable.

a. By post-hearing comment, MaryLee Fithian, Executive Director, Governor's Planning Council on Developmental Disabilities (DD) commented that no mention is made in the rule of reporting the test results both verbally and in writing to the parents or guardian. The Department commented that the method by which positive screening test results are communicated to parents or guardian of newborns is not addressed in the rule and it is the Department's recommendation that this not be addressed as most of this procedure is beyond the scope of the rule. Further, in reporting results, the Department is providing a support service to the attending physician who has the primary responsibility for providing pertinent information to his patients. The Department always provides reports of testing results directly to the physician caring for the newborn and never has direct contact with the parents and/or guardian except through the primary physician. The screening test results need interpretaion based upon the physician's diagnostic judgment which also takes into account other information and physical findings. Because this other information and physical findings are not available to the Department, it is unable to provide the necessary interpretation of results to the parents and/or guardian.

b. Several other comments raised by MaryLee Fithian of DD relate to matters not addressed in the rule. The Department commented that these matters are outside the scope of the rule and that no changes should be made therein in this regard. The Department, however, pointed out that the Division of Medical Laboratories of the Minnesota Department of Health is responsible for carrying out the laboratory work. A combination of Federal Title V SSA monies and state monies pay for the cost of the screening program. The attending physician and the parents are responsible for ensuring that referral is made for treatment should it be necessary. The Department does maintain contact with the attending physician regarding the diagnosis and treatment plan the attending physician is following, but has no authority to direct his actions.

17. Proposed rule 7 MCAR Sec. 1.172 C.3. deals with the reporting responsibility of the attending physician. The maintenance of these records by the Department is necessary for research and epidemiological purposes and to insure their treatment is initiated.

18. Proposed rule 7 MCAR Sec. 1.172 C.3.b. states that the attending physician may delegate the responsibility for reporting a confirmed diagnosis if he refers a patient with a positive screen results to a medical specialist for diagnosis and/or treatment. This section was amended in response to MaryLee Fithian's comment so that the language in the last line of proposed rule Sec. 1.172 C.3.(b) reads as follows: ". . . delegate the responsibility for reporting a confirmed diagnosis to the medical specialist." The Hearing Examiner concludes that the permissive language "may" used in this context is not unreasonable; however, it is suggested that this rule be amended to

require the attending physician making such delegation to inform the Department that further reporting shall be the responsibility of the medical specialist. The rule as modified will not constitute a substantial change and is needed and reasonable. The suggestion of the Hearing Examiner if adopted by the Department will not constitute a substantial change.

19. John F. Hick, M.D.; Robert O. Finch, M.D. by written prehearing comments and Robert S. Flom, M.D., by post-hearing comment, recommended that a state commission on genetic diseases be appointed with review authority over all Minnesota Department of Health policy decisions on genetic screening. Dr. Hick commented that many of the factors influencing decisions about genetic screening are of a moral or a psychological nature necessitating board input, not simply technical input. The existing technical Advisory Committee on Newborn Screening has been amply consulted in policy matters by the Department, but is composed only of professional advisors. Creation, in addition, of a commission on genetic diseases would provide the necessary nonprofessional and nonpartisan professional input. Dr. Hick cited the Maryland Commission as a successful prototype. On that basis, the Committee on Genetics of the American Academy of Pediatrics has recommended creation of similar commissions in other states or regions. Dr. Hick also cites the Genetic Disease Amendments of 1978 (S-2598) which serves as a further impetus to the creation of such a commission. The Department in its comments opposed the creation of such a commission. It agreed that policy decisions, such as addressed in the rules, should be made only after a board input has been obtained from both professional and lay persons. The creation of a commission is not the only method nor necessarily the best method to ensure such objectivity. The Department commented that in development of these rules, it utilized the resources of a representative cross section of concerned persons including both professional and lay people. The Department also pointed out that the development of a commission is not authorized by the statute which authorized the promulgation of this rule.

The Department pointed out in its comments, inter alia, that the screening procedures of the Department are based on the experience of investigations throughout the world, on the recommendation of leading national authorities, and on the advice of its work group composed of expert medical, laboratory and concerned lay people.

20. Darlene M. Olson, Chairperson, Governmental Affairs Committee for the Minnesota Association for Retarded Citizens, Inc., suggested that the Department expand the screening of newborns for other detectable metabolic disorders. She stated that it appears that there are six other treatable metabolic disorders that can be identified from the same blood sample. The Department commented that it is opposed to this suggestion. In determining metabolic disorders for which screening is appropriate, several criteria are used, included:

(1) Frequency of the disease in the total population to be screened,

(2) Accuracy and reliability of the screening test, and

(3) Treatability.

On the basis of the advice of an ad-hoc advisory committee composed of both professional and lay persons, the Department has determined that there is no other metabolic disorder at this time that should appropriately be added to the screening program. The Department, however, intends to annually review the current status of newborn metabolic screening program knowledge with the aid and advice of its ad-hoc advisory committee.

Based upon the foregoing Findings of Fact, the Hearing Examiner makes the following:

CONCLUSIONS

1. The Department of Health gave proper notice of the promulgation of the proposed rules.

2. The Department of Health has statutory authority to promulgate the rules.

3. The Department of Health has fulfilled all relevant substantive and procedural requirements of law or rule.

4. The modifications to the rules as discussed herein will not constitute a substantial change.

5. The Department of Health has demonstrated the need for and the reasonableness of the proposed rules by an affirmative presentation of facts in the record.

Based upon the foregoing Conclusions, the Hearing Examiner makes the following:

RECOMMENDATION

It is recommended that the proposed rules, as modified, be adopted by the Department of Health with consideration given to the Findings of Fact herein.

Dated: December 14, 1978.

Harry Seymour Crump

HARRY SEYMOUR CRUMP
Hearing Examiner

OUR FILE NO. 506

ATTORNEY GENERAL

Terry P. O'Brien
Special Assistant
Attorney General

March 1, 1979

Joanne E. Hinderaker
Special Assistant
Attorney General

296-4692

In the Matter of Proposed Amendments to 7 MCAR § 1.172 Relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

The above-captioned rule amendments have not been approved by this office for the following reasons:

1. 1.172 B. 4. references Minn. Stat. § 144.159 (1976) and thereafter quotes from that statute in a footnote. This statute was repealed in the 1978 legislative session (see: Session Laws 1978, ch. 699, sec. 17). It appears that Minn. Stat. § 144.215 (1978) is intended to replace § 144.159, however the text of the 1978 statute differs substantially from that of the 1976 law. In any case, the reference to a repealed statute in this rule is improper and the definition of "responsible party" must therefore be modified. The revision of this definition may require a resubmission of these amendments to Mr. Duane Harves for his review.

2. § 1.172 C. 2. (c) was added to the proposed rules after the hearing in response to comments made by members of the public at the hearing. In its post-hearing statement at page 2 the Department recommended the following language: "C. 2. (c) Notify the attending physician as quickly as possible, verbally and in writing, of positive screening results and provide consultation on diagnostic and treatment resources available." (emphasis added). Finding 16 of the Hearing Examiner's Report also cited this language; however the Hearing Examiner suggested that the term "as quickly as possible" was vague and should be made more specific. The Department in its Findings at #2 accepted the Hearing Examiner's recommendation and replaced "as quickly as possible" with "within 24 hours" and also added: "by deposition in first class mail" to the rule. The rule as adopted reflects these changes, however, the adopted rule also states that the attending physician must be notified "verbally or in writing by deposition in the first class mail,..." (emphasis added). As indicated above, the original amendment read "verbally and in writing" (emphasis added). The use of the conjunction "or" instead of "and" clearly changes the notification requirement in the rule. The use of "or" rather than "and" in the rule results in a requirement of only a verbal notice to the attending physician which appears to be unreasonable given the danger of the diseases involved and the difficulty in documenting such a verbal notice. Furthermore, I can find nothing in the record before this office to substantiate or justify such a major change. The

Department must provide this office with a detailed explanation if this change was an intentional one, rather than an oversight. Finally, if the conjunction "or" remains in the rule, the Department should resubmit the rule amendment to the Chief Hearing Examiner, Mr. Duane Harves, for his opinion on this issue, as it is unclear whether this matter was brought to his attention at the time of his initial review.

Following agency consideration of this memorandum, and after taking appropriate action in this regard, three copies of these rule amendments may be resubmitted to this office for approval. When resubmitting please insure that the original of the Rules as Adopted, which is necessary for filing with the Secretary of State, is resubmitted. I am returning the entire record, including the tapes, to your office although I have retained copies of all relevant materials in this matter should you wish to discuss it with me. You should contact me in reference to the question of whether a new Order Adopting Rules must be issued.

If you have any questions, do not hesitate to call me.

JEH:mb

Enclosure

cc: Duane Harves, Chief Hearing Examiner

Rules as Adopted

DEPARTMENT OF HEALTH

RULES RELATING TO TESTS OF INFANTS FOR INBORN METABOLIC ERRORS CAUSING MENTAL RETARDATION

Chapter Eleven: 7 MCAR § 1.172

The Rules published at State Register, Volume 3, Number13, pp. 679-682, October 2, 1978 (3 S.R. 679) as proposed, are adopted with the following amendments:

A. PURPOSE AND SCOPE OF THE RULE

This Rule describes the responsibilities of the hospitals, physicians and the Minnesota Department of Health to assure that all newborn infants are screened for phenylketonuria, galactosemia and hypothyroidism.

B. DEFINITIONS

For the purposes of this Rule, the following terms have the meanings given them:

1. "Attending physician" means the physician who is identified on the specimen card as the physician submitting the specimen.
2. "Newborn infant" means a child from birth through the first five days of life.
3. "Positive screening results" means that laboratory tests clearly indicate that the child has a high risk for developing one or more of the diseases covered by this Rule.
4. "Responsible party" means the administrative officer or other person in charge of each hospital where the child is born, and the person required to register the birth of a child (Minnesota Statute § 144.159, 1976*)

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* "The physician, midwife, or other legally authorized person in attendance at the birth, or if not attended, one of the parents, shall within 5 days subscribe and file a certificate of birth on a form prescribed by the Commissioner of Health for that purpose, with the local registrar of the district within which the birth occurred."

5. "Screen" means to carry out a series of laboratory tests on a dried capillary blood specimen which will identify those newborn infants who may develop phenylketonuria, galactosemia and/or hypothyroidism.

6. "Specimen" means a specimen of dried capillary blood from the newborn infant collected on a specimen card.

7. "Specimen card" means a filter paper card provided by the Minnesota Department of Health and used to collect the specimen.

C. RESPONSIBILITIES OF PARTIES INVOLVED IN THE NEWBORN METABOLIC SCREENING PROGRAM

1. The responsible party shall do all of the following:

(a) Inform the parent(s) or legal guardian that their newborn(s) will be screened for the metabolic diseases phenylketonuria, galactosemia and hypothyroidism, and explain the reasons for such screening and their right to refuse this screening on the grounds that such tests conflict with their religious tenets and practices.

(b) Collect or have collected a specimen for screening no later than the fifth day after the infant's birth, unless the parents lawfully object to such screening. If this specimen is taken prior to the third day of life or prior to 24 hours after beginning breast or milk formula feeding, the responsible party shall notify the parents or legal guardian verbally and in writing of the necessity of having the PKU test repeated on their newborn not later than the 14th day of life. If taking a blood sample at the times specified above is medically contraindicated, the sample shall be taken as soon as the infant's condition permits.

(c) Record on a permanent record the date the specimen is collected.

(d) Send the specimen and the following information to the Minnesota Department of Health laboratory within 24 hours after collection:

(1) Newborn Infant's Name

(2) Sex

(3) Mother's Name

(4) Home Address

(5) Date of Birth

(6) Date of First Feeding

(7) Date Specimen Collected

(8) Name and Address of Attending Physician and Hospital Submitting Specimen

(9) County

(10) Premature (Yes or No)

(11) Bottle Breast Both

(e) If the newborn infant is transferred to a second health care facility before the specimen is collected, the responsible party shall inform the second facility of this fact and may delegate to it the responsibility for collecting and transmitting the specimen.

2. The Minnesota Department of Health shall do all of the following:

(a) Develop specimen cards and make them available at no charge to the responsible party.

(b) Maintain a record of all cases of phenylketonuria, galactosemia and hypothyroidism reported to it.

(c) Notify the attending physician within 24 hours, verbally or in writing by deposition in first class mail, of positive screening results and provide consultation on diagnostic and treatment sources available.

3. The attending physician shall do all of the following:

(a) Report, in writing, all confirmed diagnoses of phenylketonuria, galactosemia, and hypothyroidism to:

Human Genetics Unit

Minnesota Department of Health

717 S.E. Delaware Street

Minneapolis, MN 55440

(b) If he refers a patient with positive screening results to a medical specialist for diagnosis and/or treatment, he may delegate the responsibility for reporting a confirmed diagnosis to the medical specialist.

D R A F T

TO: Terry P. O'Brien
Special Assistant
Attorney General

must have date of 3/1/79

FROM: Joanne E. Hinderaker
Special Assistant
Attorney General

RE: In the Matter of Proposed Amendments to 7 MCAR § 1.172 Relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

The above-captioned rule amendments have not been approved by this office for the following reasons:

1. 1.172 B. 4. references Minn. Stat. § 144.159 (1976) and thereafter quotes from that statute in a footnote. This statute was repealed in the 1978 legislative session (see: Session Laws 1978, ch. 699, sec. 17), ~~(1978).~~ It appears that Minn. Stat. § 144.215 (1978) is intended to replace ~~§~~ § 144.159, however the text of the 1978 statute differs substantially from that of the 1976 law. In any case, the reference to a repealed statute in this rule is improper and the definition of "responsible party" must therefore be modified. The revision of this definition may require a resubmission of these amendments to Mr. Diane Hawes for his review.

2. § 1.172 C. 2. (c) was added to the proposed rules after the hearing in response to comments made by members of the public at the hearing. In ~~the~~ its post-hearing statement at page 2 the ~~agency~~ Department recommended the following language: "C.2.(c) Notify the attending physician as quickly as possible, verbally and in writing, of positive screening results and provide consultation on diagnostic and treatment resources available." (emphasis added). Finding 16 of the Hearing Examiner's Report also cited this language; however the Hearing Examiner suggested that the term "as quickly as possible" ~~is~~ was vague and should be made more specific. The Department in its Findings at #3 accepted the Hearing Examiner's recommendation and replaced "as quickly as possible" with "within 24 hours" and also added: "by deposition in first class mail" to the rule. The rule as adopted reflects these changes, however, the adopted rule also states that the attending physician must be notified "verbally or in writing by deposition in the first class mail,..." (emphasis added). ~~Asindi~~ As indicated above, the original amendment read

"verbally and in writing" (emphasis added). The use of the conjunction "or" instead of "and" clearly changes the notification requirement in the rule. The use of "or" rather than "and" in the rule results in a requirement of only a verbal notice to the attending physician which appears to be unreasonable given the danger of the diseases involved and the difficulty in documenting such a verbal notice. Furthermore, I can find nothing in the record before this office to substantiate or justify such a major change. The Department must provide this office with a detailed explanation of this change was an intentional one, rather than an oversight. Finally, if the conjunction "or" remains in the rule, the department should resubmit the rule amendment to the Chief Hearing Examiner, Mr. Duane Harves, for his opinion on this issue, as it is unclear whether this matter was brought to his attention at the time of his initial review.

Following agency consideration of this memorandum, and after taking appropriate action in this regard, three copies of these rule amendments may be resubmitted to this office for approval. When resubmitting please insure that the original of the Rules as Adopted, which is necessary for filing with the Secretary of State, is resubmitted. I am returning the entire record, including the tapes, to this office although finally, I have retained copies of all relevant materials in this matter should you wish to discuss it with me. You should contact me in reference to the question of whether a new Order Adopting Rules must be issued.

If you have any ~~other~~ questions, do not hesitate to call me.

JEH:mb

Enclosure) mel — by this do you mean the file documents?

Because I do want the whole file to be returned to them w/ this memo!

cc: Duane Harves

ADMIN 1000

STATE OF MINNESOTA

DEPARTMENT HEALTH - PHS/MCH

Office Memorandum

RECEIVED
NOV 14 1978
OFFICE OF HEARING EXAMINERS

TO : Mr. Harry Crump
Hearing Examiner

DATE: November 14, 1978

FROM : Lee E. Schacht, Ph.D., Supervisor
Human Genetics Unit

Malcolm B. Jenkins, Ph.D., Geneticist

PHONE: 6-5269

SUBJECT: Supplemental Justification Regarding 7 MCAR §§ 1.172 Relating to the Expansion of Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

In the letter of John F. Hick, M.D., dated October 20, 1978 (State's Exhibit Number 10), the letter of Robert O. Fisch, M.D., dated November 1, 1978 (State's Exhibit Number 11) and the letter of Robert S. Flom, M.D., dated November 8, 1978, it was recommended that there be created a State Commission on Genetic Diseases. It is the Department's recommendation that such a Commission not be created in this Rule. The Department agrees that policy decisions, such as addressed in the Rule, should be made only after a broad input has been obtained from both professional and lay sources. The creation of a Commission is not the only method, nor necessarily the best method, to assure this objective. In the development of this Rule, the Department utilized the resources of a representative cross section of concerned persons including both professionals and lay people. In future revision of its genetic screening program standards, the Department plans to continue this broad input. Another consideration relative the development of a Commission is that such action is not authorized by the statute which authorized promulgation of this Rule. Thus, the creation of such a Commission is more appropriately the responsibility of the Minnesota Legislature.

In the letter of John F. Hick, M.D., dated October 20, 1978 (State's Exhibit Number 10), the letter of Robert O. Fisch, M.D., dated November 1, 1978 (State's Exhibit Number 11) and the letter of Robert S. Flom, M.D., dated November 8, 1978 support is expressed regarding the requirement that the parents be informed about the screening before a blood sample is obtained. The writers further recommend that a brochure be developed for this purpose. The Department does not recommend that this procedural matter be addressed in Rule; however, it does agree with the recommendation that it develop and make available to hospitals and physicians a brochure describing screening. It is proceeding with development of such a document. At this time it is basic public health philosophy that parents be informed of the intended screening and the significance of its results. The Department believes that this philosophy is clearly described in C.1.(a) of the Rule. The language contained therein was selected to assure consistency with the statute that authorizes this Rule.

In the letter of John F. Hick, M.D., dated October 20, 1978 (State's Exhibit Number 10), it was recommended that a section be added to C.2. (Responsibilities of the Department) relative to the Department's reporting responsibilities. The Department agrees with Dr. Hick's comments and recommends that an addition be

made to the Rule which shall state: "C.2.(c) Notify the attending physician as quickly as possible, verbally and in writing, of positive screening results and provide consultation on diagnostic and treatment resources available." This is a reasonable amendment and it is our belief that it is merely for the purpose of clarification and relates solely to a responsibility which the Department shall assume and, therefore, does not constitute a substantial change in the Rule.

In Public Exhibit Number 2, the Mayo Clinic recommends that a change be made in Section C.1.(d) to allow the performance of screening assays by laboratories other than the Department which can demonstrate competence in performing such assays. In the letters of Robert S. Flom, M.D., dated November 8, 1978, D. K. Ohrt, M.D., dated November 8, 1978, and the letter and attached resolution of Michael B. O'Sullivan, M.D., dated November 10, 1978, also express concern about Section C.1.(d) and recommend that the Department develop criteria or methods for identifying those laboratories which would be qualified to carry out the newborn metabolic screening tests. The Statement of Justification and its attached Exhibits (State's Exhibit Number 9) as well as the oral testimony of Robert A. Ulstrom, M.D., at the public hearing demonstrates sufficient basis for the Department to recommend that no change in the Rule be made.

The Department is responsible for the public health of the state. The screening of newborns for metabolic diseases which cause mental retardation if undetected and treated is a basic public health problem and concern. Accordingly, the Department must assure arrangements such that screening for identification of those newborns at risk for developing any of these diseases, is done for large numbers of newborns, is inexpensive and has a high degree of accuracy in identifying the at-risk newborn. As documented above, the centralized laboratory of the Department is the best method to assure these results.

The main thrust of Public Exhibit Number 2 is that any laboratory which meets the accreditation requirements of the College of American Pathologists or the Center for Disease Control (CDC) "should be allowed to perform those assays". The tests referred to by the Mayo Clinic are not the same as the screening tests used by the Department; the Mayo Clinic tests described are actually diagnostic tests. Unfortunately, no proficiency testing for newborn screening tests currently exists at the CDC or College of American Pathologists or anywhere else to our knowledge. The Department is presently not prepared to provide such proficiency testing and, indeed, lacks statutory authority to regulate clinical laboratory testing for newborn metabolic diseases.

We would like to emphasize that the screening procedures of the Department are based on the experience of investigations throughout the world, on the recommendations of leading national authorities, and on the advice of our work group composed of expert medical, laboratory and concerned lay people.

So as to assure that the Hearing Examiner has all information necessary to review this Rule, the Department offers the following comments relative to specific concerns in Public Exhibit Number 2.

1) On page 1, paragraph 1, the Mayo Clinic expresses concern that laboratories will not be allowed to perform assays for identification of the metabolic diseases addressed in the Rule. The Department has no intent or statutory authority to prevent any laboratory from performing whatever assay it wishes and/or is ordered by the attending physician. These assays may supplement or duplicate those performed by the Department in keeping with the requirements of this Rule.

2) On page 2, paragraph 2, the concern is addressed that analytical methods such as used by the Department typically provide a greater than 5% false positive incidence. In Exhibit A of the Justification of the Rule (State's Exhibit Number 9), it is stated that the false positive rate should not exceed approximately 1%, a condition which currently is met by the Department's pilot screening program.

3) On page 1, paragraph 3, the Mayo Clinic states that the same laboratory should perform both "baseline and follow-up assays". The Department agrees that any laboratory which performs accurate analyses should be able to provide follow-up testing. However, it does not consider this to be the major issue in assuring the usefulness of metabolic screening test results. As was pointed out in the Public Hearing testimony of Robert A. Ulstrom, M.D., and in Public Exhibit Number 1 regarding hypothyroidism screening, the accuracy of screening testing is particularly dependent on processing large numbers of specimens, thus necessitating testing by a central laboratory.

In his testimony at the Public Hearing, John F. Hick, M.D., expressed concern that screening of breast feeding infants may not detect PKU, because the breast may not initially provide enough dietary protein to elevate the blood phenylalanine level which results in positive test results. The Department does not agree with this concern and recommends that no change be made in the Rule in this regard. The minimum time in the proposed Rule is three days after birth or 24 hours after milk feeding, which we believe is sufficient to provide adequate dietary protein (Section C.1.(b)). We feel that in the hands of a competent centralized laboratory, a three-day minimum time is justified. Expert opinion on this question of optimum sample timing is somewhat varied. On the one hand, in Exhibit A of the Juftification (State's Exhibit Number 9), the recommended timing of the sample is no sooner than the fourth day of life. On the other hand, there is evidence[1,2] that the effect of feeding on PKU screening is overemphasized. To quote from the abstract of one study, "... there is no evidence that missed cases are significantly related to feeding protein or early testing in routine PKU screening of the newborn infant."[1] The Department has taken the three-day minimum elapsed time limit as a compromise between these two positions. It should be pointed out that most of the missed cases of PKU come from states where centralization of screening was not in effect.

In his letter of November 8, 1978, Thomas O. Swallen, M.D., suggests that the term "milk feeding" as used in Section C.1.(b) of the proposed Rule is ambiguous. The Department agrees and recommends that wording of line 5 of Section C.1.(b) be amended to read: "beginning breast or milk formula feeding, the responsible party shall notify the ..." It is our belief that this amendment is merely for the purpose of clarification and, therefore, does not constitute a substantial change in this Rule.

In the letters of John F. Hick, M.D., dated October 20, 1978 (State's Exhibit Number 10), Robert S. Flom, M.D., dated November 8, 1978, and Marylee Fithian, dated November 8, 1978, concern is expressed relative to the method by which positive screening test results are communicated to the parents/guardian of the newborn. The method used is not addressed in the Rule, and it is the Department's recommendation that this not be addressed as most of this procedure is beyond the scope of the Rule. In reporting results, the Department is providing a support service to the attending physician who has the primary responsibility for provision of pertinent information to his patients. The Department always provides reports of testing results directly to the physician caring for the newborn and never has direct contact with the parents/guardian except through the primary physician. The Department's communication with parents/guardian is, thus, indirect. The screening test results need interpretation based upon the physician's diagnostic judgment which also takes into account other information and physical findings. Because this other information and physical findings are not available to the Department, it is unable to provide the necessary interpretation of results to the parents/guardian.

In the letter of Marylee Fithian dated November 8, 1978, several questions are raised, relative to matters not addressed in the Rule. The Department believes these matters are outside the scope of the Rule and that no changes should be made therein in this regard. We are pleased to offer the following answers to the stated questions:

-If the parent(s) or legal guardian refuse the tests on religious grounds, what procedures must they follow to ensure the tests are not given? Likewise, if the responsible party is notified by the parent(s) or legal guardian that the tests are not to be administered for religious reasons, what steps is the responsible party to take?

Once the parents/guardian have informed the responsible party of their refusal, no further action is required on their part. When the responsible party is informed of the parents/guardian refusal, he should act in keeping with the procedures of the hospital in which the infant was born. The Department suggests that documentation of refusal be recorded in the patient's chart.

-Who is responsible for carrying out the laboratory work?

At the present time, the Division of Medical Laboratories of the Department.

-Who pays for the tests?

A combination of Federal Title V SSA monies and state monies pays for the cost of the screening program.

-How will costs be determined?

The costs of the various laboratory procedures are calculated from a formula developed by the Center for Disease Control of the U. S. Public Health Service.

-Likewise, no mention is made concerning who is responsible for ensuring that referral is made for treatment, should it be necessary.

This is the responsibility of the attending physician and the parents. The Department does maintain contact with the attending physician regarding the diagnosis and treatment plan the attending physician is following, but has no authority to direct his actions.

In her letter of November 8, 1978, Marylee Fithian also suggests a change in language at the last line of C.3.(b) so that the Rule reads: "...Delegate the responsibility for reporting a confirmed diagnosis to the medical specialist." The Department agrees with this amendment and recommends its adoption. The Department believes that this amendment is merely for the purpose of clarification and, therefore, does not constitute a substantial change in this Rule.

In the letter of Darlene M. Olson, dated November 7, 1978, concern was expressed that Minnesota was "... not staying in the forefront of health care in this area..." referring screening for other treatable metabolic disorders. The Department does not feel that there are other metabolic disorders for which it should be screening at this time and, accordingly, no change of the Rule is needed. In determining metabolic disorders for which screening is appropriate, several criteria are used, including: 1) frequency of the disease in the total population to be screened, 2) accuracy and reliability of the screening test, and 3) treatability. On the basis of the advice of an ad hoc advisory group comprised of both professionals and lay persons, the Department has determined that there are no other metabolic disorders at this time that should appropriately be added to its screening program. The Department is, however, aware of the rapidly changing "state of the art" in this regard and, accordingly, intends to annually review the current status of newborn metabolic screening program knowledge with the aid and advice of its ad hoc advisory group. When it is determined that the newborn metabolic screening program should be expanded to include other disorders, this Rule will be amended for that purpose.

In his testimony at the public hearing, Henry Homburger, M.D., stated his concern relative to the possibility that the same centralization of laboratory services being recommended in the newborn metabolic screening program may be applied to other kinds of laboratory screening tests in the future. The Department only wishes to amend this Rule to bring Minnesota's newborn metabolic screening program into agreement with the recommendations that have been made nationally and locally. The Department does not plan, nor dies it have the authority to use this Rule revision now to centralize laboratory testing procedures other than those related to screening of newborns for inborn errors of metabolism.

In the letter of Thomas O. Swallen, M.D., of November 10, 1978, concern is expressed about Section C.1.(b) which requires a repeat screening test for PKU not later than the 14th day of life. He recommends that this be amended so that the repeat test for PKU, when necessary, "can be provided as soon as is reasonably convenient, and preferably before the 14th day of life." He recommends this language so that retesting can be done at the first usual office visit of the newborn infant, usually four to six weeks after birth. The Department cannot accept this recommendation. If the screening test is delayed until the fourth to sixth week after birth, treatment of the affected infant will also be delayed which could result in permanent damage to the infant. The Department bases its conclusion in part upon the recommendations of the American Academy of Pediatrics (Public Exhibit Number 9, Exhibit A).

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[1] V. K. Dontaville and G. C. Cunningham 1973 Effect of feeding on screening for PKU in infants. Pediatrics, 51, 531

[2] H. Hansen 1975 Prevention of mental retardation due to PKU: selected aspects of program validity. Preventive Medicine, 4, 310.

LES:MBJ:djc:jm

STATE OF MINNESOTA

COUNTY OF HENNEPIN

BEFORE THE MINNESOTA

COMMISSIONER OF HEALTH

In the Matter of Proposed Amendments to 7 MCAR § 1.172 Relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

FINDINGS OF FACT, CONCLUSIONS, AND ORDER

The above-entitled matter came on for hearing at 9:30 a.m. on November 6, 1978, in Room 105 of the Minnesota Department of Health Building, 717 Delaware Street Southeast, in Minneapolis, Minnesota. The Commissioner of Health received the Report of the Hearing Examiner, submitted by Harry Seymour Crump, Hearing Examiner, which report was dated December 14, 1978.

Based upon all the testimony, exhibits, written comments and the Report of the Hearing Examiner, the Commissioner now makes the following:

FINDINGS OF FACT

The Commissioner adopts, as his own, the findings of facts contained in the Report of the Hearing Examiner dated December 14, 1978, said report being fully incorporated into and made a part of these findings as if set forth by the Commissioner, except that the Commissioner does not adopt such findings of fact to the extent that they are inconsistent with the following:

1. In accordance with the statement of the Hearing Examiner in Findings of Fact #10 of the Report of the Hearing Examiner, dated December 14, 1978 (hereinafter "Report") that the duplication of the language of Minn. Stat. § 144.159 is crucial to those affected by the proposed rule, a footnote to 7 MCAR § 1.172B.4 quoting statutory language shall remain in the rule as finally adopted.

2. In accordance with the recommendation of the Hearing Examiner contained in the second paragraph of Finding #16 of the Report

concerning the vagueness of the term "as quickly as possible," 7 MCAR § 1.172C.2. is amended by deleting the term "as quickly as possible," and replacing it with the phrase "within 24 hours." Furthermore, so as to clarify the nature of the notification, the phrase "by deposition in first class mail" shall be inserted following the word "writing."

3. In accordance with Finding #18 of the Report, the use of the permissive language "may" used in the context of 7 MCAR § 1.172C.3.b. is not unreasonable.

4. In Finding #18 of the Report, the Hearing Examiner suggests that 7 MCAR § 1.172C.3.b. be amended to require that a physician who delegates to a medical specialist the responsibility for reporting a confirmed diagnosis to the Health Department inform the Minnesota Department of Health of such delegation. The Hearing Examiner did not believe such a rule would constitute a substantial change. In view of the fact that such a requirement was not addressed in the original Notice of Hearing, it is conceivable that such a mandatory duty placed upon physicians would have invited reaction at the public hearing. Indeed, the addition of a new duty imposed upon a physician by the Department of Health's rule which was not contemplated in the original Notice of Hearing nor in comments submitted while the record was open could arguably result in a rule substantially different from that raised by the Notice of Hearing. The Commissioner does not address the merits as to whether such an amendment constitutes a substantial change. Since the issue as to substantial change in this instance is sufficiently clouded and controversial, the Commissioner does not amend the rule so as to impose upon physicians a new mandate to report. The rule as finally adopted shall not so mandate.

CONCLUSIONS OF LAW

The Commissioner adopts as his own, the conclusions contained in the Report of the Hearing Examiner, dated December 14, 1978, said conclusions being fully incorporated and made a part of the Commissioner's conclusions as if set forth by the Commissioner.

ORDER

The amendments to 7 MCAR § 1.172 relating to tests of infants for inborn metabolic errors causing mental retardation are found to be reasonable, necessary, and supported by the evidence contained in the records, and are hereby approved and adopted pursuant to authority vested in me by Minn. Stat. §§ 144.125, 144.05(a)(b) and (c), 144.12, and 144.06 (1978), except that said rules shall be modified in accordance with non-substantial changes as they are set forth in the Commissioner's Findings of Fact herein.

Dated: January 19, 1979.

STATE OF MINNESOTA

COMMISSIONER OF HEALTH

WARREN R. LAWSON, M.D.
Acting Commissioner

RULES AS PROPOSED

MINNESOTA DEPARTMENT OF HEALTH

RULES OF THE MINNESOTA DEPARTMENT OF HEALTH RELATING TO THE EXPANSION OF TESTS OF INFANTS FOR INBORN METABOLIC ERRORS CAUSING MENTAL RETARDATION

CHAPTER ELEVEN: 7 MCAR §§ 1.172

~~Testing for Phenylketonuria~~

~~(a) Prescribed Test (Screening) Procedure. The Guthrie Inhibitation Assay procedure is specified as a procedure to be used for screening for phenylketonuria. The laboratories of the Minnesota Department of Health will provide the test, without charge, and will furnish necessary materials for submission of specimens, request forms and instructions to hospitals and physicians. Other laboratories, including hospital laboratories, may carry out this test or other approved test, providing they meet the specifications designated by the State Department of Health. Specimens from cases where doubtful or positive findings are obtained will be submitted to the State Department of Health Laboratories for confirmation and follow-up.~~

~~All suspected or confirmed cases of phenylketonuria shall be reported to the State Department of Health.~~

~~Other tests for screening of inborn errors of metabolism leading to mental retardation may be designated and provided by the laboratories of the State Department of Health, in cooperation with the Minnesota State Medical Association and the Minnesota Society of Clinical Pathologists.~~

~~(b) Time and Place for Testing~~

~~(1) Each institution wherein initial newborn care is rendered shall test or have tested each newborn infant for phenylketonuria. Blood for the test shall be collected on the day of discharge for the institution provided that such discharge does not occur prior to the third day of life or prior~~

to 24 hours after the commencement of milk feedings. If discharge occurs prior to either or both of these times, the institution shall notify the parents or legal guardian verbally and in writing of the necessity of having the PKU test performed on their child not later than the 14th day of life. If the PKU test is medically contraindicated at the times specified above, the test shall be performed as soon as the medical condition of the infant permits such testing.

(2) Infants receiving domiciliary care in the institution wherein initial newborn care was rendered or who are transferred to another institutuion for specialized care was rendered or who are transferred to another institution for specialized care, shall be tested not later than the 14th day of life, unless medically contraindicated, in which case the test shall be performed as soon as the medical condition of the infant permits such testing.

(3) When an infant has been born outside of an institution and has not subsequently been admitted to an institution for intial newborn care, it shall be the duty of the person required by section 144.159 of Minnesota Statutes 1961 to register the birth of a child to cause the test to be administered not later than the 14th day of life, unless medically contra indicated, inwhich case the test shall be performed as soon as the medical condition of the infant permits such testing.

(e) Duties of Administrator of Responsible Institution and of the Person Required to Register the Birth of a Child. The administrator of the respon sible insitutuion and the person required to register the birth of a child shall.

(1) within 24 hours after the taking of the specimen, cause such speci men to be fowarded to the designated laboratory by first class mail or its equivalent;

(2) cause to be recorded on the infant's chart the date of taking of the test specimen;

(3) cause the results of the test for phenylketonuria performed as prescribed by the State Board of Health to be recorded on the infant's chart.

(4) notify the mother in writing that early discharge from hospital or insufficient milk feeding or late breast feeding may make the test invalid and that it is her responsibility to have the infant retested by the physician at 4 to 6 weeks of age at the first postpartum or clinical visit.

(d) Postnatal Visit. It is recommended at the first postnatal visit to the attending physician or to the well child clinic at approximately 4-6 weeks of age, each newborn should be retested.

(e) Definitive Diagnosis. In the event of a positive test, the State Health Department Laboratory will send to the physician (or hospital) materials for submission of specimens for confirmatory diagnosis.

A. PURPOSE AND SCOPE OF THE RULE

This Rule describes the responsibilities of the hospitals, physicians and the Minnesota Department of Health to assure that all newborn infants are screened for phenylketonuria, galactosemia and hypothyroidism.

B. DEFINITIONS

For the purposes of this Rule, the following terms have the meanings given them:

1. "Attending physician" means the physician who is identified on the specimen card as the physician submitting the specimen.
2. "Newborn infant" means a child from birth through the first five days of life.
3. "Positive screening results" means that laboratory tests clearly indicate that the child has a high risk for developing one or more of the diseases covered by this Rule.

4. "Responsible party" means the administrative officer or other person in charge of each hospital where the child is born, and the person required to register the birth of a child (Minnesota Statute §§ 144.159, 1976*)

5. "Screen" means to carry out a series of laboratory tests on a dried capillary blood specimen which will identify those newborn infants who may develop phenylketonuria, galactosemia and/or hypothyroidism.

6. "Specimen" means a specimen of dried capillary blood from the newborn infant collected on a specimen card.

7. "Specimen card" means a filter paper card provided by the Minnesota Department of Health and used to collect the specimen.

C. RESPONSIBILITIES OF PARTIES INVOLVED IN THE NEWBORN METABOLIC SCREENING PROGRAM

1. The responsibile party shall do all of the following:

(a) Inform the parent(s) or legal guardian that their newborn(s) will be screened for the metabolic diseases phenylketonuria, galactosemia and hypothyroidism, and explain the reasons for

---

* "The physician, midwife, or other legally authorized person in attendance at the birth, or if not attended, one of the parents, shall within 5 days subscribe and file a certificate of birth on a form prescribed by the Commissioner of Health for that purpose, with the local registrar of the district within which the birth occurred."

such screening and their right to refuse this screening on the grounds that such tests conflict with their religious tenets and practices.

(b) Collect or have collected a specimen for screening no later than the fifth day after the infant's birth, unless the parents lawfully object to such screening. If this specimen is taken prior to the third day of life or prior to 24 hours after beginning milk feeding, the responsible party shall notify the parents or legal guardian verbally and in writing of the necessity of having the PKU test repeated on their newborn not later than the 14th day of life. If taking a blood sample at the times specified above is medically contraindicated, the sample shall be taken as soon as the infant's condition permits.

(c) Record on a permanent record the date the specimen is collected.

(d) Send the specimen and the following information to the Minnesota Department of Health laboratory within 24 hours after collection:

(1) Newborn Infant's Name

(2) Sex

(3) Mother's Name

(4) Home Address

(5) Date of Birth

(6) Date of First Feeding

(7) Date Specimen Collected

(8) Name and Address of Attending Physician and Hospital Submitting Specimen

(9) County

(10) Premature (Yes or No)

(11) Bottle Breast Both

(e) If the newborn infant is transferred to a second health care facility before the specimen is collected, the responsible party shall inform the second facility of this fact and may delegate to it the responsibility for collecting and transmitting the specimen.

2. The Minnesota Department of Health shall do all of the following:

(a) Develop specimen cards and make them available at no charge to the responsible party.

(b) Maintain a record of all cases of phenylketonuria, galactosemia and hypothyroidism reported to it.

3. The attending physician shall do all of the following:

(a) Report, in writing, all confirmed diagnosis of phenylketonuria, galactosemia, and hypothyroidism to:

Human Genetics Unit
Minnesota Department of Health
717 S.E. Delaware Street
Minneapolis, MN 55440

(b) If he refers a patient with positive screening results to a medical specialist for diagnosis and/or treatment, he may delegate the responsibility for reporting a confirmed diagnosis.

JUSTIFICATION OF REVISION OF 7 MCAR § 1.172,
"TESTING FOR PHENYLKETONURIA"

A. Authority, Purpose and Scope

The proposed revision of 7 MCAR § 1.172 expands the screening of newborn infants to include galactosemia and hypothyroidism. Authority for this revision is found in Minnesota Statute 144.125.

The feasibility of newborn screening for inborn diseases causing mental retardation is determined by (1) the predictive value and costs of the screening test employed, (2) the incidence of the disease, and (3) efficacy of treatment. Also of particular relevance is tha fact that many such conditions in newborns are not readily diagnosed on clinical grounds alone, and, by the time clinical signs do become overt, permanent mental retardation has occurred. Galactosemia and congenital hypothyroidism are two conditions which fulfill the criteria of feasibility for newborn screening. (See Exhibit A, attached hereto and made a part hereof.)

This section is necessary to introduce the rule to the reader and provide a general summary of the subject of the rule.

B. Definitions

1. Attending Physician. This definition is necessary in order to identify the physician who has the responsibility to comply with this rule.

2. Newborn infant. This definition is necessary to avoid confusion with the usual definition of "neonatal", i.e., the first four weeks after birth. Since, after birth there is an immediate and progressive effect of the diseases tested for, it is imperative that they be screened for as soon as is practical. For logistic reason, five days is a practical limit for time after birth before a sample is taken for screening.

3. Positive screening result. This definition is necessary to clarify the interpretation of the laboratory tests.

4. Responsible party. This definition is necessary to identify individuals responsible for providing parents of newborns with an explanation of the implications of the screening tests and obtaining their consent, and for submitting a specimen for screening.

5. Screen. This definition is necessary to clarify the function of the laboratory tests. In most cases these are not regarded as diagnostic tests; further, confirmatory tests are needed. The screen simply indicates individuals in a high risk category.

6. Specimen. This definition is necessary to standardize the type and quantity of sample used for laboratory analysis.

7. Specimen card. Since different filter papers give different results in the tests, this definition is necessary in order to standardize the types of filter paper used to convey the specimen to the laboratory. Also, because the proposed MCAR 1.172 (C) indicates all specimens must be sent to the Minnesota Health Department, this definition provides a standard form for recording patient information and for reporting results.

C. Responsibilities of Parties Involved in the Newborn Metabolic Screening Program

1. (a) This section is included in order to comply with Minnesota Statute 144.125, which states

> "The provision of this section shall not apply to any infant whose parents object thereto on the grounds that such tests and treatment conflict with their religious tenets and practices."

In order for parents to exercise their right to refusal, it is necessary that they receive prior explanation of why the screening tests are to be performed on their newborn infants. Thus, performance of the screening tests is contingent on having a concise explanation of the importance of performing these tests. This explanation is most easily provided within a few days of birth under the direction of the responsible party.

1. (b) Since after birth there is an immediate and progressive effect of the diseases, it is imperative that they be screened for as soon as is practical. Five days after birth is a reasonable limit for elapsed time before a sample is taken for screening.

If the specimen is taken too soon after birth or before institution of milk feeding, the level of blood phenylalanine may not rise enough to be detected by screening. Thus it is necessary that a second specimen be obtained. As the persons most responsible for the newborn infant, it is reasonable that the responsibility for obtaining a second specimen lies with the parents. This information is supplied to the parents/guardians in writing by the responsible party as described in C.1.(b).

1. (c) Recording of this date is necessary since validity of the results depends on the time interval between birth and the taking of sample.

1. (d) The importance of the central laboratory in newborn metabolic screening has been stressed. (See Exibit B, attached hereto and made a part hereof.) The chief reasons are (1) improved quality of results, and (2) lower cost per test. In order to maximize the

efficiency and accuracy of screening in Minnesota all newborn specimens will be sent to the Minnesota Department of Health as described in MDH 1.172 C.1.(d).

Since after birth there is an immediate and progressive effect of the diseases, it is imperative that they be screened for as soon as possible. It is obvious that the sooner the samples are received, the sooner the screening can be performed. For logistic reasons, 24 hours delay in sending the collected specimens is felt to be a reasonable maximum.

The informational items 1-11 of this section are necessary to provide for accurate interpretation of the test results and for prompt. complete reporting of these results.

1. (e) This section clarifies the responsibility for screening in instances where an infant changes primary care facilities soon after birth.

2. This section describes the role of the Minnesota Department of Health in newborn screening. A record of all Minnesota cases of PKU, galactosemia, and hypothyroidism is necessary for research and epidemiological purposes and to insure that treatment is instituted. Therefore, this record shall be kept at the Minnesota Department of Health as described in Section C.2.(b).

3. (a) This section assures that all cases of PKU, galactosemia, and hypothyroidism can be recorded by the Minnesota Department of Health. Such recording is necessary for research and epidemiological purposes and to insure that treatment is instituted.

3. (b) This section clarifies the responsibility of reporting cases of PKU, galactosemia, and hypothyroidism to the Minnesota Department of Health in instances where the attending physician may not b be involved with diagnosis of the newborn.

ADMIN 1000 (Rev. 1/78)

STATE OF MINNESOTA

DEPARTMENT ATTORNEY GENERAL - Health

Office Memorandum

TO : Lee Sheehy
Special Assistant
Attorney General
G25 Administration

DATE: February 8, 1979

FROM : Richard A. Wexler
Assistant Attorney General

PHONE: 6-5370

SUBJECT: Documents in Support of Proposed Amendments to 7 MCAR § 1.172 Relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

Enclosed for your review are three files containing documentation in support of the above-referenced rules. I am submitting this material on behalf of Terry O'Brien who represented the Department during the promulgation process. He asked me to submit the rules while he was on annual leave. It is my understanding that the rules were not very controversial and I believe the documents are self-explanatory. Essentially, the rules merely delete old rules relating to testing for PKU and provide new rules to test for PKU to include new metabolic errors which could cause disease in children. The minor changes which are evidenced in the rules as finally proposed are not substantial and did not provide controversy from the public, the hearing examiners's office or Terry.

A transcript was not made of this hearing inasmuch as there was no request for one by either department personnel or the public. I am, however, enclosing the tape recordings of the hearing.

If you have any questions concerning these documents, please contact Terry upon his return. He will be back in the office on Tuesday, February 20, 1979. (If something comes up prior to February 20 which needs an immediate response, please give me a call. I am not familiar with the rules but will try to get any information you may need.) Thank you.

RAW:sil

Enclosures

cc: Dr. Lee Schacht

STATE OF MINNESOTA

COUNTY OF HENNEPIN

BEFORE THE MINNESOTA

COMMISSIONER OF HEALTH

In the Matter of Proposed
Amendments to 7 MCAR § 1.172
Relating to Tests of Infants for
Inborn Metabolic Errors Causing
Mental Retardation

ORDER FOR HEARING

To effectively implement Minn. Stat. § 144.125 (1976) the Minnesota Commissioner of Health deems it necessary to consider adoption of the proposed amendments to 7 MCAR § 1.172 captioned above pursuant to the authority vested in him by the above-referenced statute and by Minn. Stat. §§ 144.12 (Supp. 1977) and 144.05 (1976).

NOW, THEREFORE, IT IS ORDERED this 13 day of September, 1978, that a public hearing on the proposed rules captioned above be held in the Board Room, Minnesota Department of Health Building, 717 Delaware Street Southeast, Minneapolis, Minnesota, on Monday, November 6, 1978, commencing at 9:30 a.m., and continuing until all persons or representatives of associations or other interested groups have had an opportunity to be heard.

IT IS FURTHER ORDERED, that notice of said hearing be published in the State Register and be given to all persons or representatives of associations or other interested groups who have registered their names with the Secretary of State for that purpose and to all persons who are presently members of the Minnesota Legislature.

STATE OF MINNESOTA

COMMISSIONER OF HEALTH

WARREN R. LAWSON, M.D.
Commissioner of Health

STATE OF MINNESOTA

COUNTY OF HENNEPIN

BEFORE THE MINNESOTA

COMMISSIONER OF HEALTH

In the Matter of Proposed
Amendments to 7 MCAR § 1.172
Relating to Tests of Infants for
Inborn Metabolic Errors Causing
Mental Retardation

NOTICE OF HEARING

Notice is hereby given that a public hearing in the above-entitled matter will be held pursuant to Minn. Stat. § 15.0412, subd. 4 (Supp. 1977), in the Board Room, Minnesota Department of Health Building, 717 Delaware Street Southeast, Minneapolis, Minnesota, on Monday, November 6, 1978, commencing at 9:30 a.m.

All interested or affected persons will have an opportunity to participate concerning the adoption of the proposed amendments to 7 MCAR § 1.172 captioned above. Statements may be made orally and written material may be submitted. In addition, whether or not an appearance is made at the hearing, written statements or material may be submitted by mail to Harry Crump, Hearing Examiner, at Room 300, 1745 University Avenue, Saint Paul, Minnesota 55104, telephone (612) 296-8111, either before the hearing or within five (5) working days after the close of the hearing or for a longer period not to exceed 20 calendar days if ordered by the hearing examiner. All such statements will be entered into and become part of the record. Testimony or other evidence to be submitted for consideration should be pertinent to the matter at hand. For those wishing to submit written statements or exhibits, it is requested that at least three (3) copies be furnished. In addition, it is suggested, to save time and avoid duplication, that those persons, organizations, or associations having a common viewpoint or interest in these proceedings join together where possible and present a single statement in

behalf of such interests. The conduct of the hearing shall be governed by the rules of the Office of Hearing Examiners.

A copy of the proposed amendments is attached hereto and made a part hereof.

Copies of the proposed amendments are now available and at least one free copy may be obtained by writing to the Supervisor of the Human Genetics Unit, Minnesota Department of Health, 717 Delaware Street Southeast, Minneapolis, Minnesota 55440. Additional copies will be available at the door on the date of the hearing.

The statutory authority of the Commissioner of Health to promulgate and adopt these rules is contained in Minn. Stat. § 144.125 (1976).

In addition, please be advised that Minn. Stat. ch. 10A requires each lobbyist to register with the State Ethical Practices Board within five (5) days after he commences lobbying. A lobbyist is defined in Minn. Laws 1978, ch. 463, § 11 as any individual:

> (a) Engaged for pay or other consideration, or authorized by another individual or association to spend money, who spends more than five hours in any month or more than $250, not including his own travel expenses and membership dues, in any year, for the purpose of attempting to influence legislative or administrative action by communicating or urging others to communicate with public officials; or
>
> (b) Who spends more than $250, not including his own traveling expenses and membership dues, in any year for the purpose of attempting to influence legislative or administrative action by communicating or urging others to communicate with public officials.

The statute provides certain exceptions. Questions should be directed to the Ethical Practices Board, 41 State Office Building, Saint Paul, Minnesota 55155, telephone (612) 296-5615.

Notice: Any person may request notification of the date on which the hearing examiner's report will be available, after which date the agency may not take any final action on the rules for a period of five working days. Any person may request notification of the date on which the hearing record has been submitted (or resubmitted) to the Attorney General by the agency. If you desire to be so notified, you may so indicate at the hearing. After the hearing, you may request notification by sending a written request to the hearing examiner (in the case of the hearing examiner's report), or to the agency (in the case of the agency's submission or resubmission to the Attorney General).

Notice is hereby given that 25 days prior to the hearing, a statement of need and reasonableness will be available for review at the agency and at the Office of Hearing Examiners. This statement of need and reasonableness will include a summary of all of the evidence which will be presented by the agency at the hearing justifying both the need for and the reasonableness of the proposed rule/rules. Copies of the statement of need and reasonableness may be obtained from the Office of Hearing Examiner at a minimal charge.

Dated: September 13, 1978

STATE OF MINNESOTA

COMMISSIONER OF HEALTH



WARREN R. LAWSON, M.D.
Commissioner of Health

STATE OF MINNESOTA

COUNTY OF HENNEPIN

BEFORE THE MINNESOTA

COMMISSIONER OF HEALTH

In the Matter of Proposed Amendments to 7 MCAR § 1.172 Relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

STATEMENT OF NUMBER OF PERSONS EXPECTED TO ATTEND AND LENGTH OF HEARING

The number of persons expected to attend the hearing in the above-captioned matter is twenty.

It is estimated that one hour will be necessary for agents of the Minnesota Department of Health to present evidence at the hearing.

Dated: September 13, 1978

STATE OF MINNESOTA

COMMISSIONER OF HEALTH

WARREN R. LAWSON, M.D.
Commissioner of Health

STATE OF MINNESOTA

COUNTY OF HENNEPIN

BEFORE THE MINNESOTA

COMMISSIONER OF HEALTH

In the Matter of Proposed
Amendments to 7 MCAR § 1.172
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A copy of the proposed amendments is attached hereto and made a part hereof.

Copies of the proposed amendments are now available and at least one free copy may be obtained by writing to the Supervisor of the Human Genetics Unit, Minnesota Department of Health, 717 Delaware Street Southeast, Minneapolis, Minnesota 55440. Additional copies will be available at the door on the date of the hearing.

The statutory authority of the Commissioner of Health to promulgate and adopt these rules is contained in Minn. Stat. § 144.125 (1976).

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(b) Who spends more than $250, not including his own traveling expenses and membership dues, in any year for the purpose of attempting to influence legislative or administrative action by communicating or urging others to communicate with public officials.

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Notice is hereby given that 25 days prior to the hearing, a statement of need and reasonableness will be available for review at the agency and at the Office of Hearing Examiners. This statement of need and reasonableness will include a summary of all of the evidence which will be presented by the agency at the hearing justifying both the need for and the reasonableness of the proposed rule/rules. Copies of the statement of need and reasonableness may be obtained from the Office of Hearing Examiner at a minimal charge.

Dated: September 13, 1978

STATE OF MINNESOTA

COMMISSIONER OF HEALTH

/s/ Warren R. Lawson
WARREN R. LAWSON, M.D.
Commissioner of Health

MINNESOTA DEPARTMENT OF HEALTH

RULES OF THE MINNESOTA DEPARTMENT OF HEALTH RELATING TO THE EXPANSION OF TESTS OF INFANTS FOR INBORN METABOLIC ERRORS CAUSING MENTAL RETARDATION

CHAPTER ELEVEN: 7 MCAR §§ 1.172

Testing for Phenylketonuria

(a) Prescribed Test (Screening) Procedure. The Guthrie Inhibitation Assay procedure is specified as a procedure to be used for screening for phenylketonuria. The laboratories of the Minnesota Department of Health will provide the test, without charge, and will furnish necessary materials for submission of specimens, request forms and instructions to hospitals and physicians. Other laboratories, including hospital laboratories, may carry out this test or other approved test, providing they meet the specifications designated by the State Department of Health. Specimens from cases where doubtful or positive findings are obtained will be submitted to the State Department of Health Laboratories for confirmation and follow up.

All suspected or confirmed cases of phenylketonuria shall be reported to the State Department of Health.

Other tests for screening of inborn errors of metabolism leading to mental retardation may be designated and provided by the laboratories of the State Department of Health, in cooperation with the Minnesota State Medical Association and the Minnesota Society of Clinical Pathologists.

(b) Time and Place for Testing

(1) Each institution wherein initial newborn care is rendered shall test or have tested each newborn infant for phenylketonuria. Blood for the test shall be collected on the day of discharge for the institution provided that such discharge does not occur prior to the third day of life or prior

to 24 hours after the commencement of milk feedings. If discharge occurs prior to either or both of these times, the institution shall notify the parents or legal guardian verbally and in writing of the necessity of having the PKU test performed on their child not later than the 14th day of life. If the PKU test is medically contraindicated at the times specified above, the test shall be performed as soon as the medical condition of the infant permits such testing.

(2) Infants receiving domiciliary care in the institution wherein initial newborn care was rendered or who are transferred to another institutuion for specialized care was rendered or who are transferred to another institution for specialized care, shall be tested not later than the 14th day of life, unless medically contreindicated, in which case the test shall be performed as soon as the medical condition of the infant permits such testing.

(3) When an infant has been born outside of an institution and has not subsequently been admitted to an institution for intial newborn care, it shall be the duty of the person required by section 144.159 of Minnesota Statutes 1961 to register the birth of a child to cause the test to be administered not later than the 14th day of life, unless medically contra indicated, inwhich case the test shall be performed as soon as the medical condition of the infant permits such testing.

(c) Duties of Administrator of Responsible Institution and of the Person Required to Register the Birth of a Child. The administrator of the respon sible insitutuion and the person required to register the birth of a child shall:

(1) within 24 hours after the taking of the specimen, cause such speci men to be fowarded to the designated laboratory by first class mail or its equivalent;

(2) cause to be recorded on the infant's chart the date of taking of the test specimen;

(3) cause the results of the test for phenylketonuria performed as prescribed by the State Board of Health to be recorded on the infant's chart.

(4) notify the mother in writing that early discharge from hospital or insufficient milk feeding or late breast feeding may make the test invalid and that it is her responsibility to have the infant retested by the physician at 4 to 6 weeks of age at the first postpartum or clinical visit.

(d) Postnatal Visit. It is recommended at the first postnatal visit to the attending physician or to the well child clinic at approximately 4-6 weeks of age, each newborn should be retested.

(e) Definitive Diagnosis. In the event of a positive test, the State Health Department Laboratory will send to the physician (or hospital) materials for submission of specimens for confirmatory diagnosis.

A. PURPOSE AND SCOPE OF THE RULE

This Rule describes the responsibilities of the hospitals, physicians and the Minnesota Department of Health to assure that all newborn infants are screened for phenylketonuria, galactosemia and hypothyroidism.

B. DEFINITIONS

For the purposes of this Rule, the following terms have the meanings given them:

1. "Attending physician" means the physician who is identified on the specimen card as the physician submitting the specimen.
2. "Newborn infant" means a child from birth through the first five days of life.
3. "Positive screening results" means that laboratory tests clearly indicate that the child has a high risk for developing one or more of the diseases covered by this Rule.

4. "Responsible party" means the administrative officer or other person in charge of each hospital where the child is born, and the person required to register the birth of a child (Minnesota Statute §§ 144.159, 1976*)

5. "Screen" means to carry out a series of laboratory tests on a dried capillary blood specimen which will identify those newborn infants who may develop phenylketonuria, galactosemia and/or hypothyroidism.

6. "Specimen" means a specimen of dried capillary blood from the newborn infant collected on a specimen card.

7. "Specimen card" means a filter paper card provided by the Minnesota Department of Health and used to collect the specimen.

C. RESPONSIBILITIES OF PARTIES INVOLVED IN THE NEWBORN METABOLIC SCREENING PROGRAM

1. The responsibile party shall do all of the following:

(a) Inform the parent(s) or legal guardian that their newborn(s) will be screened for the metabolic diseases phenylketonuria, galactosemia and hypothyroidism, and explain the reasons for

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* "The physician, midwife, or other legally authorized person in attendance at the birth, or if not attended, one of the parents, shall within 5 days subscribe and file a certificate of birth on a form prescribed by the Commissioner of Health for that purpose, with the local registrar of the district within which the birth occurred."

such screening and their right to refuse this screening on the grounds that such tests conflict with their religious tenets and practices.

(b) Collect or have collected a specimen for screening no later than the fifth day after the infant's birth, unless the parents lawfully object to such screening. If this specimen is taken prior to the third day of life or prior to 24 hours after beginning milk feeding, the responsible party shall notify the parents or legal guardian verbally and in writing of the necessity of having the PKU test repeated on their newborn not later than the 14th day of life. If taking a blood sample at the times specified above is medically contraindicated, the sample shall be taken as soon as the infant's condition permits.

(c) Record on a permanent record the date the specimen is collected.

(d) Send the specimen and the following information to the Minnesota Department of Health laboratory within 24 hours after collection:

(1) Newborn Infant's Name

(2) Sex

(3) Mother's Name

(4) Home Address

(5) Date of Birth

(6) Date of First Feeding

(7) Date Specimen Collected

(8) Name and Address of Attending Physician and Hospital Submitting Specimen

(9) County

(10) Premature (Yes or No)

(11) Bottle Breast Both

(e) If the newborn infant is transferred to a second health care facility before the specimen is collected, the responsible party shall inform the second facility of this fact and may delegate to it the responsibility for collecting and transmitting the specimen.

2. The Minnesota Department of Health shall do all of the following:

(a) Develop specimen cards and make them available at no charge to the responsible party.

(b) Maintain a record of all cases of phenylketonuria, galactosemia and hypothyroidism reported to it.

3. The attending physician shall do all of the following:

(a) Report, in writing, all confirmed diagnosis of phenylketonuria, galactosemia, and hypothyroidism to:

Human Genetics Unit
Minnesota Department of Health
717 S.E. Delaware Street
Minneapolis, MN 55440

(b) If he refers a patient with positive screening results to a medical specialist for diagnosis and/or treatment, he may delegate the responsibility for reporting a confirmed diagnosis.

JUSTIFICATION OF REVISION OF 7 MCAR § 1.172,
"TESTING FOR PHENYLKETONURIA"

A. Authority, Purpose and Scope

The proposed revision of 7 MCAR § 1.172 expands the screening of newborn infants to include galactosemia and hypothyroidism. Authority for this revision is found in Minnesota Statute 144.125.

The feasibility of newborn screening for inborn diseases causing mental retardation is determined by (1) the predictive value and costs of the screening test employed, (2) the incidence of the disease, and (3) efficacy of treatment. Also of particular relevance is tha fact that many such conditions in newborns are not readily diagnosed on clinical grounds alone, and, by the time clinical signs do become overt, permanent mental retardation has occurred. Galactosemia and congenital hypothyroidism are two conditions which fulfill the criteria of feasibility for newborn screening. (See Exhibit A, attached hereto and made a part hereof.)

This section is necessary to introduce the rule to the reader and provide a general summary of the subject of the rule.

B. Definitions

1. Attending Physician. This definition is necessary in order to identify the physician who has the responsibility to comply with this rule.

2. Newborn infant. This definition is necessary to avoid confusion with the usual definition of "neonatal", i.e., the first four weeks after birth. Since, after birth there is an immediate and progressive effect of the diseases tested for, it is imperative that they be screened for as soon as is practical. For logistic reason, five days is a practical limit for time after birth before a sample is taken for screening.

3. Positive screening result. This definition is necessary to clarify the interpretation of the laboratory tests.

4. Responsible party. This definition is necessary to identify individuals responsible for providing parents of newborns with an explanation of the implications of the screening tests and obtaining their consent, and for submitting a specimen for screening.

5. Screen. This definition is necessary to clarify the function of the laboratory tests. In most cases these are not regarded as diagnostic tests; further, confirmatory tests are needed. The screen simply indicates individuals in a high risk category.

6. Specimen. This definition is necessary to standardize the type and quantity of sample used for laboratory analysis.

7. Specimen card. Since different filter papers give different results in the tests, this definition is necessary in order to standardize the types of filter paper used to convey the specimen to the laboratory. Also, because the proposed MCAR 1.172 (C) indicates all specimens must be sent to the Minnesota Health Department, this definition provides a standard form for recording patient information and for reporting results.

C. Responsibilities of Parties Involved in the Newborn Metabolic Screening Program

1. (a) This section is included in order to comply with Minnesota Statute 144.125, which states

> "The provision of this section shall not apply to any infant whose parents object thereto on the grounds that such tests and treatment conflict with their religious tenets and practices."

In order for parents to exercise their right to refusal, it is necessary that they receive prior explanation of why the screening tests are to be performed on their newborn infants. Thus, performance of the screening tests is contingent on having a concise explanation of the importance of performing these tests. This explanation is most easily provided within a few days of birth under the direction of the responsible party.

1. (b) Since after birth there is an immediate and progressive effect of the diseases, it is imperative that they be screened for as soon as is practical. Five days after birth is a reasonable limit for elapsed time before a sample is taken for screening.

If the specimen is taken too soon after birth or before institution of milk feeding, the level of blood phenylalanine may not rise enough to be detected by screening. Thus it is necessary that a second specimen be obtained. As the persons most responsible for the newborn infant, it is reasonable that the responsibility for obtaining a second specimen lies with the parents. This information is supplied to the parents/guardians in writing by the responsible party as described in C.1.(b).

1. (c) Recording of this date is necessary since validity of the results depends on the time interval between birth and the taking of sample.

1. (d) The importance of the central laboratory in newborn metabolic screening has been stressed. (See Exibit B, attached hereto and made a part hereof.) The chief reasons are (1) improved quality of results, and (2) lower cost per test. In order to maximize the

efficiency and accuracy of screening in Minnesota all newborn specimens will be sent to the Minnesota Department of Health as described in MDH 1.172 C.1.(d).

Since after birth there is an immediate and progressive effect of the diseases, it is imperative that they be screened for as soon as possible. It is obvious that the sooner the samples are received, the sooner the screening can be performed. For logistic reasons, 24 hours delay in sending the collected specimens is felt to be a reasonable maximum.

The informational items 1-11 of this section are necessary to provide for accurate interpretation of the test results and for prompt. complete reporting of these results.

1. (e) This section clarifies the responsibility for screening in instances where an infant changes primary care facilities soon after birth.

2. This section describes the role of the Minnesota Department of Health in newborn screening. A record of all Minnesota cases of PKU, galactosemia, and hypothyroidism is necessary for research and epidemiological purposes and to insure that treatment is instituted. Therefore, this record shall be kept at the Minnesota Department of Health as described in Section C.2.(b).

3. (a) This section assures that all cases of PKU, galactosemia, and hypothyroidism can be recorded by the Minnesota Department of Health. Such recording is necessary for research and epidemiological purposes and to insure that treatment is instituted.

3. (b) This section clarifies the responsibility of reporting cases of PKU, galactosemia, and hypothyroidism to the Minnesota Department of Health in instances where the attending physician may not b be involved with diagnosis of the newborn.

Equation #8:

$$\Delta H = (U_0 - U_1) \times A$$

Where

U_0 = The U-Value for the existing door assembly before improvement;

U_1 = The U-Value for the proposed door assembly after improvement;

A = The area of the door assembly in square feet separating conditioned space from unconditioned space.

2 MCAR § 1.16209 General payback equation. The payback period in years shall be calculated by dividing the cost of the energy-saving improvement by the product of the price per unit of energy and the quantity of annual energy savings. The payback equation shall be:

Equation B:

$$T = \frac{C}{(P) \times (\Delta E)}$$

Where

T = payback period in years;

C = the total cost of purchasing and installing energy saving improvements minus applicable federal and/or state tax credits, grants or subsidies;

P = price per unit of energy, this unit being the same as the unit of annual energy savings, ΔE. The appropriate values of P shall be those certified by the director of the Minnesota Energy Agency in the *State Register*, pursuant to Minn. Stat. Section 116H.129, Subd. 1 (1977 Supplement), as amended by Minn. Laws 1978, c. 786, Section 2;

ΔE = the quantity of annual energy savings in the appropriate energy units, e.g., hundreds of cubic feet of natural gas, gallons of fuel oil, or kilowatt-hours of electricity, as calculated for each of the energy efficiency standards.

Department of Health Human Genetics Division

Proposed Rules Relating to the Expansion of Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

Notice of Hearing

Notice is hereby given that a public hearing in the above-entitled matter will be held pursuant to Minn. Stat. § 15.0412, subd. 4 (Supp. 1977), in the Board Room, Minnesota Department of Health Building, 717 Delaware Street Southeast, Minneapolis, Minnesota, on Monday, November 6, 1978, commencing at 9:30 a.m.

All interested or affected persons will have an opportunity to participate concerning the adoption of the proposed amendments to 7 MCAR § 1.172 captioned above. Statements may be made orally and written material may be submitted. In addition, whether or not an appearance is made at the hearing, written statements or material may be submitted by mail to Harry Crump, Hearing Examiner, at Room 300, 1745 University Avenue, Saint Paul, Minnesota 55104, telephone (612) 296-8111, either before the hearing or within five (5) working days after the close of the hearing or for a longer period not to exceed 20 calendar days if ordered by the hearing examiner. All such statements will be entered into and become part of the record. Testimony or other evidence to be submitted for consideration should be pertinent to the matter at hand. For those wishing to submit written statements or exhibits, it is requested that at least three (3) copies be furnished. In addition, it is suggested, to save time and avoid duplication, that those persons, organizations, or associations having a common viewpoint or interest in these proceedings join together where possible and present a single statement in behalf of such interests. The conduct of the hearing shall be governed by the rules of the Office of Hearing Examiners.

A copy of the proposed amendments is attached hereto and made a part hereof.

Copies of the proposed amendments are now available and at least one free copy may be obtained by writing to the Supervisor of the Human Genetics Unit, Minnesota Department of Health, 717 Delaware Street Southeast, Min-

KEY: RULES SECTION — Underlining indicates additions to proposed rule language. ~~Strike outs~~ indicate deletions from proposed rule language. **PROPOSED RULES SECTION** — Underlining indicates additions to existing rule language. ~~Strike outs~~ indicate deletions from existing rule language. If a proposed rule is totally new, it is designated "all new material."

neapolis, Minnesota 55440. Additional copies will be available at the door on the date of the hearing.

The statutory authority of the Commissioner of Health to promulgate and adopt these rules is contained in Minn. Stat. § 144.125 (1976).

In addition, please be advised that Minn. Stat. ch. 10A requires each lobbyist to register with the State Ethical Practices Board within five (5) days after he commences lobbying. A lobbyist is defined in Laws of 1978, ch. 463, § 11 as any individual:

(a) Engaged for pay or other consideration, or authorized by another individual or association to spend money, who spends more than five hours in any month or more than $250, not including his own travel expenses and membership dues, in any year, for the purpose of attempting to influence legislative or administrative action by communicating or urging others to communicate with public officials; or

(b) Who spends more than $250, not including his own traveling expenses and membership dues, in any year for the purpose of attempting to influence legislative or administrative action by communicating or urging others to communicate with public officials.

The statute provides certain exceptions. Questions should be directed to the Ethical Practices Board, 41 State Office Building, Saint Paul, Minnesota 55155, telephone (612) 296-5615.

Notice: Any person may request notification of the date on which the hearing examiner's report will be available, after which date the agency may not take any final action on the rules for a period of five working days. Any person may request notification of the date on which the hearing record has been submitted (or resubmitted) to the Attorney General by the agency. If you desire to be so notified, you may so indicate at the hearing. After the hearing, you may request notification by sending a written request to the hearing examiner (in the case of the hearing examiner's report), or to the agency (in the case of the agency's submission or resubmission to the Attorney General).

Notice is hereby given that 25 days prior to the hearing, a statement of need and reasonableness will be available for review at the agency and at the Office of Hearing Examiners. This statement of need and reasonableness will include a summary of all of the evidence which will be presented by the agency at the hearing justifying both the need for and the reasonableness of the proposed rule/rules. Copies of the statement of need and reasonableness may be obtained from the Office of Hearing Examiner at a minimal charge.

September 13, 1978

Warren R. Lawson, M.D.
Commissioner of Health

Rules as Proposed

Chapter Eleven

7 MCAR § 1.172

~~Testing for Phenylketonuria~~

~~(a) Prescribed Test (Screening) Procedure. The Guthrie Inhibitation Assay procedure is specified as a procedure to be used for screening for phenylketonuria. The laboratories of the Minnesota Department of Health will provide the test, without charge, and will furnish necessary materials for submission of specimens, request forms and instructions to hospitals and physicians. Other laboratories, including hospital laboratories, may carry out this test or other approved test, providing they meet the specifications designated by the State Department of Health. Specimens from cases where doubtful or positive findings are obtained will be submitted to the State Department of Health Laboratories for confirmation and follow-up.~~

~~All suspected or confirmed cases of phenylketonuria shall be reported to the State Department of Health.~~

~~Other tests for screening of inborn errors of metabolism leading to mental retardation may be designated and provided by the laboratories of the State Department of Health, in cooperation with the Minnesota State Medical Association and the Minnesota Society of Clinical Pathologists.~~

~~(b) Time and Place for Testing~~

~~(1) Each institution wherein initial newborn care is rendered shall test or have tested each newborn infant for phenylketonuria. Blood for the test shall be collected on the day of discharge for the institution provided that such discharge does not occur prior to the third day of life or prior to 24 hours after the commencement of milk feedings. If discharge occurs prior to either or both of these times, the institution shall notify the parents or legal guardian verbally and in writing of the necessity of having the PKU test performed on their child not later than the 14th day of life. If the PKU test is medically contraindicated at the times specified above, the test shall be performed as soon as the medical condition of the infant permits such testing.~~

~~(2) Infants receiving domiciliary care in the institution wherein initial newborn care was rendered or who are transferred to another institution for specialized care was rendered or who are transferred to another institution for specialized care, shall be tested not later than the 14th day of life, unless medically contraindicated, in which case the test shall be performed as soon as the medical condition of the infant permits such testing.~~

~~(3) When an infant has been born outside of an in-~~

~~stitution and has not subsequently been admitted to an institution for initial newborn care, it shall be the duty of the person required by section 144.159 of Minnesota Statutes 1961 to register the birth of a child to cause the test to be administered not later than the 14th day of life, unless medically contraindicated, in which case the test shall be performed as soon as the medical condition of the infant permits such testing.~~

~~(c) Duties of Administrator of Responsible Institution and of the Person Required to Register the Birth of a Child. The administrator of the responsible institution and the person required to register the birth of a child shall:~~

~~(1) within 24 hours after the taking of the specimen, cause such specimen to be forwarded to the designated laboratory by first class mail or its equivalent;~~

~~(2) cause to be recorded on the infant's chart the date of taking of the test specimen;~~

~~(3) cause the results of the test for phenylketonuria performed as prescribed by the State Board of Health to be recorded on the infant's chart.~~

~~(4) notify the mother in writing that early discharge from hospital or insufficient milk feeding or late breast feeding may make the test invalid and that it is her responsibility to have the infant retested by the physician at 4 to 6 weeks of age at the first postpartum or clinical visit.~~

~~(d) Postnatal Visit. It is recommended at the first postnatal visit to the attending physician or to the well child clinic at approximately 4-6 weeks of age, each newborn should be retested.~~

~~(e) Definitive Diagnosis. In the event of a positive test, the State Health Department Laboratory will send to the physician (or hospital) materials for submission of specimens for confirmatory diagnosis.~~

A. Purpose and scope of the rule. This rule describes the responsibilities of the hospitals, physicians and the Minnesota Department of Health to assure that all newborn infants are screened for phenylketonuria, galactosemia and hypothyroidism.

B. Definitions. For the purposes of this rule, the following terms have the meanings given them:

1. "Attending physician" means the physician who is identified on the specimen card as the physician submitting the specimen.

2. "Newborn infant" means a child from birth through the first five days of life.

3. "Positive screening results" means that laboratory tests clearly indicate that the child has a high risk for developing one or more of the diseases covered by this rule.

4. "Responsible party" means the administrative officer or other person in charge of each hospital where the child is born, and the person required to register the birth of a child (Minn. Stat. § 144.159, 1976*)

5. "Screen" means to carry out a series of laboratory tests on a dried capillary blood specimen which will identify those newborn infants who may develop phenylketonuria, galactosemia and/or hypothyroidism.

6. "Specimen" means a specimen of dried capillary blood from the newborn infant collected on a specimen card.

7. "Specimen card" means a filter paper card provided by the Minnesota Department of Health and used to collect the specimen.

C. Responsibilities of parties involved in the Newborn Metabolic Screening Program.

1. The responsible party shall do all of the following:

a. Inform the parent(s) or legal guardian that their newborn(s) will be screened for the metabolic diseases phenylketonuria, galactosemia and hypothyroidism, and explain the reasons for such screening and their right to refuse this screening on the grounds that such tests conflict with their religious tenets and practices.

b. Collect or have collected a specimen for screening no later than the fifth day after the infant's birth, unless the parents lawfully object to such screening. If this specimen is taken prior to the third day of life or prior to 24 hours

* "The physician, midwife, or other legally authorized person in attendance at the birth, or if not attended, one of the parents, shall within 5 days subscribe and file a certificate of birth on a form prescribed by the Commissioner of Health for that purpose, with the local registrar of the district within which the birth occurred."

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after beginning milk feeding, the responsible party shall notify the parents or legal guardian verbally and in writing of the necessity of having the PKU test repeated on their newborn not later than the 14th day of life. If taking a blood sample at the times specified above is medically contraindicated, the sample shall be taken as soon as the infant's condition permits.

c. Record on a permanent record the date the specimen is collected.

d. Send the specimen and the following information to the Minnesota Department of Health laboratory within 24 hours after collection:

(1) Newborn Infant's Name

(2) Sex

(3) Mother's Name

(4) Home Address

(5) Date of Birth

(6) Date of First Feeding

(7) Date Specimen Collected

(8) Name and Address of Attending Physician and Hospital Submitting Specimen

(9) County

(10) Premature (Yes or No)

(11) Bottle Breast Both

e. If the newborn infant is transferred to a second health care facility before the specimen is collected, the responsible party shall inform the second facility of this fact and may delegate to it the responsibility for collecting and transmitting the specimen.

2. The Minnesota Department of Health shall do all of the following:

a. Develop specimen cards and make them available at no charge to the responsible party.

b. Maintain a record of all cases of phenylketonuria, galactosemia and hypothyroidism reported to it.

3. The attending physician shall do all of the following:

a. Report, in writing, all confirmed diagnosis of phenylketonuria, galactosemia, and hypothyroidism to:

Human Genetics Unit
Minnesota Department of Health
717 S.E. Delaware Street
Minneapolis, MN 55440

b. If he refers a patient with positive screening results to a medical specialist for diagnosis and/or treatment, he may delegate the responsibility for reporting a confirmed diagnosis.

STATE OF MINNESOTA

COUNTY OF HENNEPIN

BEFORE THE MINNESOTA

COMMISSIONER OF HEALTH

In the Matter of Proposed
Amendments to 7 MCAR § 1.172
Relating to Tests of Infants for
Inborn Metabolic Errors Causing
Mental Retardation

STATEMENT OF EVIDENCE

The Commissioner of Health (hereinafter "Commissioner") will introduce the following evidence at the hearing in the above-entitled matter scheduled for Monday, November 6, 1978, commencing at 9:30 a.m. in the Board Room, Minnesota Department of Health Building, 717 Delaware Street Southeast, Minneapolis, Minnesota.

1. Documents attached hereto and made a part hereof evidencing the Commissioner's compliance with procedural requirements for rule making:

(a) Order for Hearing;

(b) Notice of Hearing as mailed;

(c) Affidavit of Receipt of the Secretary of State's List;

(d) Certificate of the Secretary of State; and

(e) Affidavit of Mailing of the Notice of Hearing.

2. Documents attached hereto and made a part hereof constituting the Commissioner's affirmative presentation of facts establishing the need for and reasonableness of the proposed amendments and evidencing the Commissioner's compliance with substantive requirements for rule making:

(a) Statement of Need; and

(b) Statement of Facts Establishing Reasonableness of Amendments, entitled "Justification for Amendments to 7 MCAR § 1.172."

The following witnesses will represent the Commissioner at the hearing:

Ronald G. Campbell, M.D.
Chief, Section of Maternal and Child Health

Malcolm B. Jenkins, Ph.D.
Geneticist

Dwayne Morse, Dr.P.H.
Director, Medical Laboratories

Lee E. Schacht, Ph.D.
Supervisor, Human Genetics Unit

Richard P. Nelson, M.D.
Chief, Section of Crippled Childrens Services

Said witnesses will be available to answer questions as they might relate to the Commissioner's affirmative presentation of facts as set forth through the previously listed and attached documents.

The Statement of Need attached hereto contains the citations to the Commissioner's statutory authority to promulgate the proposed amendments to the Commissioner's rules.

Dated: October 11, 1978

STATE OF MINNESOTA

COMMISSIONER OF HEALTH

WARREN R. LAWSON, M.D.
Commissioner of Health

STATE OF MINNESOTA

COUNTY OF HENNEPIN

BEFORE THE MINNESOTA

COMMISSIONER OF HEALTH

In the Matter of Proposed
Amendments to 7 MCAR § 1.172
Relating to Tests of Infants for
Inborn Metabolic Errors Causing
Mental Retardation

STATEMENT OF NEED

The need to adopt the above-captioned amendments to rules arises in order to update current rules so as to reflect technological advances in testing for certain disorders and to permit the Department of Health to more fully comply with legislation. Minn. Stat. § 144.125 (1976) requires that persons in charge of institutions caring for infants twenty-eight days or less of age and those required to register children's births:

> Cause to have administered to every such infant or child in its or his care tests for phenylketonuria and other inborn errors of metabolism causing mental retardation in accordance with rules or regulations prescribed by the state board of health.

At the time that 7 MCAR § 1.172 was last revised, a cost effective method of screening tests for phenylketonuria (hereinafter "PKU") existed. However, the contemporaneous technology did not include screening tests for galactosemia and hypothyroidism, diseases which are inborn errors of metabolism causing mental retardation and which may cause death and/or irreversible mental retardation if not diagnosed and treated as soon as feasibile after birth.

As a result of advances in the science and art of screening procedures, it is now technically possible and economically cost effective to screen for galactosemia and hypothyroidism as well as PKU. Inasmuch as the Minnesota Department of Health now has the capacity to test for galactosemia and

hypothyroidism with the same specimen which is currently tested for PKU, an amendment to the rule is necessary in order to reflect this advance, facilitate prompt diagnosis and to insure prompt treatment of children with these conditions. Of course, it is much more economical for the state to perform tests to screen children to determine the presence of these conditions than it is to conceivably care for a child who was not identified as having these conditions in a timely manner.

Minn. Stat. § 144.125 (1976) states in relevant part as follows:

> Testing and the recording and reporting of such results of such tests (for inborn errors of metabolism causing mental retardation) shall be performed at such times and in such manner as may be prescribed by the state board of health.

Approximately sixty thousand births occur in the state of Minnesota every year. In addition to the initial screening necessary for every child born within the state, reevaluation or retesting may have to be performed on an additional five to ten thousand specimens. Thus, there is an obvious advantage to be gained in centralization of testing inasmuch as the tests are more effective and cost efficient if centralized due to the large numbers of testing procedures performed. The need to prescribe the centralization of testing and the recording of such tests results from a need to insure uniformity with respect to the procedures of screening tests, uniformity with respect to the standards of such tests, uniformity of record keeping, uniformity of the storage of specimens and uniformity of follow-up procedures with respect to children tested. Furthermore, the capability and the experience of people performing these tests increases as more tests are performed, and the central testing authority can better institute quality control inasmuch as all tests will be performed at the same location and under the same authority. Centralization of testing is also necessary in order to have a central location for the records necessary for research performed in cooperation with appropriate scientific and medical authorities. Inasmuch as the state of the art in definitive diagnosis and treatment is constantly changing, the usefulness of a central pool or location of records is obvious. The uniformity prescribed in these rules, as well as the centralization of the screening, testing, and recording of the results of such tests, are needed to assure adequate follow-up to those children who need follow-up and to insure that high risk children are diagnosed and maintained in appropriate treatment programs as long as necessary.

Further legal authority to support amendments to the rule may be found in Minn. Stat. § 144.05(a)(b) and (c) (1976). Unquestionably, requiring the submission of specimens in order to uniformly screen for the presence of PKU, galactosemia and hypothyroidism constitutes the collection and analysis of health data, and helps to identify and describe a recognized health problem, and helps to plan, facilitate, coordinate, provide and support the organization of services for the prevention, if caught in time, and the control of PKU, galactosemia and hypothyroidism and the limitation of disabilities resulting from these diseases.

Furthermore, Minn. Stat. § 144.12 (1976) authorizes the Commissioner of Health to promulgate regulations for the preservation of the public health. Submission of specimens and the centralization of reporting and recording of PKU, galactosemia and hypothyroidism helps to perserve the public health. Also, requiring the submission of specimens of newly born infants and the centralization of testing such specimens falls within the provisions of Minn. Sat. § 144.06 (1976) authorizing the Commissioner of Health to provide instruction and advice to mothers and their infants after childbirth.

Further need for the promulgation of the amendments to 7 MCAR § 1.172 may be found in the Statement of Facts Establishing Reasonableness of the Amendments entitled, "Justification for Amendments to 7 MCAR § 1.172".

Dated: October 11, 1978

STATE OF MINNESOTA

COMMISSIONER OF HEALTH



WARREN R. LAWSON, M.D.
Commissioner of Health

JUSTIFICATION OF REVISION OF 7 MCAR § 1.172,
"TESTING FOR PHENYLKETONURIA"

A. Authority, Purpose and Scope

The proposed revision of 7 MCAR § 1.172 expands the screening of newborn infants to include galactosemia and hypothyroidism. Authority for this revision is found in Minnesota Statute 144.125.

The feasibility of newborn screening for inborn diseases causing mental retardation is determined by (1) the predictive value and costs of the screening test employed, (2) the incidence of the disease, and (3) efficacy of treatment. Also of particular relevance is tha fact that many such conditions in newborns are not readily diagnosed on clinical grounds alone, and, by the time clinical signs do become overt, permanent mental retardation has occurred. Galactosemia and congenital hypothyroidism are two conditions which fulfill the criteria of feasibility for newborn screening. (See Exhibit A, attached hereto and made a part hereof.)

This section is necessary to introduce the rule to the reader and provide a general summary of the subject of the rule.

B. Definitions

1. Attending Physician. This definition is necessary in order to identify the physician who has the responsibility to comply with this rule.

2. Newborn infant. This definition is necessary to avoid confusion with the usual definition of "neonatal", i.e., the first four weeks after birth. Since, after birth there is an immediate and progressive effect of the diseases tested for, it is imperative that they be screened for as soon as is practical. For logistic reason, five days is a practical limit for time after birth before a sample is taken for screening.

3. Positive screening result. This definition is necessary to clarify the interpretation of the laboratory tests.

4. Responsible party. This definition is necessary to identify individuals responsible for providing parents of newborns with an explanation of the implications of the screening tests and obtaining their consent, and for submitting a specimen for screening.

5. Screen. This definition is necessary to clarify the function of the laboratory tests. In most cases these are not regarded as diagnostic tests; further, confirmatory tests are needed. The screen simply indicates individuals in a high risk category.

6. Specimen. This definition is necessary to standardize the type and quantity of sample used for laboratory analysis.

7. Specimen card. Since different filter papers give different results in the tests, this definition is necessary in order to standardize the types of filter paper used to convey the specimen to the laboratory. Also, because the proposed MCAR 1.172 (C) indicates all specimens must be sent to the Minnesota Health Department, this definition provides a standard form for recording patient information and for reporting results.

C. Responsibilities of Parties Involved in the Newborn Metabolic Screening Program

1. (a) This section is included in order to comply with Minnesota Statute 144.125, which states

> "The provision of this section shall not apply to any infant whose parents object thereto on the grounds that such tests and treatment conflict with their religious tenets and practices."

In order for parents to exercise their right to refusal, it is necessary that they receive prior explanation of why the screening tests are to be performed on their newborn infants. Thus, performance of the screening tests is contingent on having a concise explanation of the importance of performing these tests. This explanation is most easily provided within a few days of birth under the direction of the responsible party.

1. (b) Since after birth there is an immediate and progressive effect of the diseases, it is imperative that they be screened for as soon as is practical. Five days after birth is a reasonable limit for elapsed time before a sample is taken for screening.

If the specimen is taken too soon after birth or before institution of milk feeding, the level of blood phenylalanine may not rise enough to be detected by screening. Thus it is necessary that a second specimen be obtained. As the persons most responsible for the newborn infant, it is reasonable that the responsibility for obtaining a second specimen lies with the parents. This information is supplied to the parents/guardians in writing by the responsible party as described in C.1.(b).

1. (c) Recording of this date is necessary since validity of the results depends on the time interval between birth and the taking of sample.

1. (d) The importance of the central laboratory in newborn metabolic screening has been stressed. (See Exibit B, attached hereto and made a part hereof.) The chief reasons are (1) improved quality of results, and (2) lower cost per test. In order to maximize the

efficiency and accuracy of screening in Minnesota all newborn specimens will be sent to the Minnesota Department of Health as described in MDH 1.172 C.1.(d).

Since after birth there is an immediate and progressive effect of the diseases, it is imperative that they be screened for as soon as possible. It is obvious that the sooner the samples are received, the sooner the screening can be performed. For logistic reasons, 24 hours delay in sending the collected specimens is felt to be a reasonable maximum.

The informational items 1-11 of this section are necessary to provide for accurate interpretation of the test results and for prompt. complete reporting of these results.

1. (e) This section clarifies the responsibility for screening in instances where an infant changes primary care facilities soon after birth.

2. This section describes the role of the Minnesota Department of Health in newborn screening. A record of all Minnesota cases of PKU, galactosemia, and hypothyroidism is necessary for research and epidemiological purposes and to insure that treatment is instituted. Therefore, this record shall be kept at the Minnesota Department of Health as described in Section C.2.(b).

3. (a) This section assures that all cases of PKU, galactosemia, and hypothyroidism can be recorded by the Minnesota Department of Health. Such recording is necessary for research and epidemiological purposes and to insure that treatment is instituted.

3. (b) This section clarifies the responsibility of reporting cases of PKU, galactosemia, and hypothyroidism to the Minnesota Department of Health in instances where the attending physician may not b be involved with diagnosis of the newborn.

PEDIATRICS • VOLUME 60 • NUMBER 3 • SUPPLEMENT

Screening for Congenital Metabolic Disorders in the Newborn Infant: Congenital Deficiency of Thyroid Hormone and Hyperphenylalaninemia

Committee on Genetics

Charles R. Scriver, M.D., Chairman; Murray Feingold, M.D.; Peter Mamunes, M.D.; *and* Henry L. Nadler, M.D.

Consultants: Barton Childs, M.D.; Jean H. Dussault, M.D.; Neil A. Holtzman, M.D.; Parvin Justice, Ph.D.; *and* Rueben Matalon, M.D.

The Committee on Genetics of the American Academy of Pediatrics was formed in 1976. The initial reports from the Committee are published in this supplement to *Pediatrics:* one on guidelines for screening the newborn infant for hyperphenylalaninemia (including phenylketonuria [PKU]) and the other on screening for congenital hypothyroidism.

The first statement describes guidelines for screening for thyroid hormone deficiency in newborn infants; it concerns a traditional problem in pediatrics, the prevention of cretinism. A statement on "T_4 screening" has already been issued by the American Thyroid Association.[1] Why is there need for another (and longer) statement from the Academy? The Task Force on Genetic Screening recommended a special review of T_4 screening, and that recommendation has been acted on quickly in the hope that most of the mistakes made in PKU screening will not be repeated in T_4 screening. The American Thyroid Association statement adequately describes the status of testing for T_4 deficiency; it does not cover other essential components of an effective screening program, namely, provision for serving patients, retrieval, diagnosis, and treatment. The Committee urges pediatricians and endocrinologists who elect to push ahead with T_4 testing to pause and examine the many issues of mass newborn infant screening before they act too hastily, perhaps to the detriment of their patients and newborn infant screening programs.

Dr. Jean Dussault served as consultant to the Committee when it examined T_4 screening; his personal experience extends to ¼ million screened subjects and emanates from a model program which has largely avoided many pitfalls of newborn infant screening. After reviewing that experience and examining it with the existing problems of PKU screening in mind,[2] the Committee could not recommend universal (mass) T_4 screening for a region in the absence of an advisory committee and an integrated screening program with supporting services.

The statement on screening for hyperphenylalaninemia was prepared by Dr. Neil A. Holtzman; it is intended to help pediatricians and their associates avoid the pitfalls surrounding newborn screening, which are delineated in the report from the National Academy of Sciences on Genetic Screening.[2] Screening for hyperphenylalaninemia is still evolving as an effective public health activity. For example, a newly recognized form of PKU caused by dihydropteridine reductase deficiency was discovered long after screening programs for neonatal hyperphenylalaninemia were well instituted. It is now essential to distinguish this variant from other causes of hyperphenylalaninemia for purposes of prognosis, treatment, and counseling; this imposes new requirements for backup services on the screening programs. The need for a regional commission or an advisory committee[2-4] to guide the development of new resources and to evaluate the performance of existing services is one of the lessons learned from past experience with PKU screening.[1]

This screening supplement does not consider screening for other congenital metabolic disorders which may be of interest to pediatricians, e.g., galactosemia, cystic fibrosis, and maple syrup urine disease. The principal reason for not making additional statements now is our belief that the regional advisory committees or commissions can make these decisions about implementation of "add-on" screening tests. The capabilities for the region will depend on the organization of the existing screening program. If a regional commission does not exist, the committee urges those responsible for the screening programs to familiarize themselves with the concept[2-4] and to act accordingly.

REFERENCES

1. Newborn Committee of the American Thyroid Association: Recommendations for screening programs for congenital hypothyroidism. J Pediatr 89:692, 1976.
2. National Academy of Sciences: Genetic Screening: Programs, Principles and Research. Washington, DC, National Academy of Sciences, 1975.
3. Task Force on Genetic Screening: The pediatrician and genetic screening (every pediatrician a geneticist). *Pediatrics* 58:737, 1976.

ACKNOWLEDGMENT

The Committee acknowledges the advice and assistance of Dr. Reuben Matalon, Dr. Parvin Justice, and Dr. Jean Lockhart, Director, Department of Committees of the American Academy of Pediatrics.

Screening for Congenital Deficiency of Thyroid Hormone

The Task Force on Genetic Screening was not able to discuss details of the various forms of genetic and metabolic screening.[1] A Committee on Genetics was formed to examine these and other issues relating to congenital disease and medical genetics. The following statement is one of the Committee's reports.

Congenital thyroid hormone deficiency is a prime example of a condition whose early diagnosis, as well as the opportunity for effective treatment, can be missed. The following report examines both the practice of newborn infant screening for early diagnosis of congenital thyroid hormone (T_4) deficiency and the relation of that activity to the principles of metabolic (and genetic) screening.[2] The reader is also referred to a parallel statement prepared by a committee of the American Thyroid Association.[3]

BACKGROUND INFORMATION

There is limited placental transport of thyrotropin (TSH) and the thyroid hormones 3,5,3′-triiodothyronine (T_3) and thyroxine (T_4). Serum T_4 concentration in the newborn infant will be diminished when there is congenital deficiency of thyroid tissue, impaired activity of one of the enzymes involved in thyroid hormone biosynthesis (T_4 hormone dysgenesis), deficient serum T_4 binding globulin (TBG), or deficient stimulation of thyroid (by TSH) or pituitary (by thyrotropin releasing hormone [TRH]). Primary congenital hypothyroidism (cretinism) is associated with a high frequency of mental retardation; cretinism accounts for about 1% to 2% of admissions to institutions for the mentally retarded. Only half of the patients with cretinism achieve IQs above 90 if diagnosis and treatment are delayed until 3 to 6 months of age, but 75% of patients achieve this outcome when clinical diagnosis is made and treatment begins before 3 months of age.[4] It has yet to be determined whether diagnosis and treatment within the first month of life can further improve the outcome.

An accurate radioimmunoassay system is available to measure T_4 concentration in body fluids; a corresponding assay is also available to measure TSH in body fluids. Accordingly, newborn infant screening for congenital hypothyroidism is now possible. The combined application of the T_4 and TSH assay facilitates newborn infant screening and enhances specificity and sensitivity of the process. (Specificity and sensitivity have precise meanings in screening terminology. *Specificity* is the ability of the screening test to exclude normal subjects from false detections. *Sensitivity* is the ability of the screening test to detect subjects with the abnormality.) The objective of T_4 screening in newborn infants is to obtain early diagnosis and initiate treatment at the incipient stage of hypothyroidism.

Many infants (in fact, 425,000) have already been screened for T_4 deficiency in five pilot programs. (The five programs were carried out in Quebec, 250,000 infants; New England, 70,000; Oregon, 64,000; Pittsburgh, 25,000; and Toronto, 16,000. These data are valid up to September 1976.[5]) Among these, 72 infants (or 1 in 5,900 live births) were confirmed to have primary or secondary congenital hypothyroidism and 6 others have inherited defects in the biosynthesis of T_4 (dyshormonogenesis). However, at least 36 additional infants (31.6%) have TBG deficiency as the cause for their positive T_4 screening test results. The total number of infants with a diagnosed cause for decreased serum T_4 concentration is 114 in the 425,000 tested in these pilot programs, of which 68.4% required specific treatment. Only two patients with congenital hypothyroidism have apparently been missed in these screening programs: one infant escaped diagnosis because he was not actually screened (apparent sensitivity = 78/80 for the screening programs); the other was missed by the test (apparent sensitivity = 78/79 for the test). This is an excellent, effective, early "track record" for a new form of mass screening of newborn infants; the record indicates a requirement for an effective screening program and a reliable test.

T_4 SCREENING: DETAILS

The technical aspects of T_4 testing and screening are critical for its success. Attention to details, both for the test and the program, accounts for the acceptable sensitivity of the initial pilot programs.

Tests

The T_4 radioimmunoassay can be applied either to dried blood spots on filter paper (Schleicher and Schull, No. 903)—collected from a heel prick or from cord blood—or to serum. One of the two recommended assays[6,7] should be used.

The TSH radioimmunoassay[7,8] can also be done on the filter paper blood specimen or on serum. Specificity of screening is augmented and economic costs are reduced when the TSH assay is applied to the same sample evincing a low T_4 level.

Measurement of reverse T_3 in blood or serum is unlikely to be a useful adjunct for newborn infant screening.[5]

The use of heel prick blood obtained at discharge from the nursery is recommended in preference to cord blood samples; specificity of the T_4 and TSH tests is better on heel prick blood.[3,5]

Specificity

False-positive test results (i.e., low T_4 levels without deficient gland activity or TBG deficiency) will occur. The lowest possible frequency of such results (highest specificity) is an essential objective of an effective T_4 screening program. Experience indicates[10] that 1.84% of filter-paper samples yield a "low" T_4 concentration (positive test). A low value by the assay applied to filter-paper, heel-blood samples is defined as a value less than 2.3 SD from the geometric mean for the day,[10] uncorrected for the weight of the infant.[11] Such precision in the cutoff level for delineation of a "low" T_4 concentration can be obtained only in a laboratory processing many samples daily under rigorously standardized conditions. The majority (98.4%) of these "positive" test results are false-positive.[10]

Attention to the birth weight of the infant permits a corrective factor to be applied, which reduces the frequency of false-positive T_4 test results by 0.15%.[11] The age of the infant does not influence the T_4 test result. A further reduction in the frequency of false-positive test results follows the application of TSH assay to the 1.84% of samples with a low T_4 value. A TSH concentration greater than 1.0 μU on filter-paper spots of heel blood indicates a "positive" test. When T_4 values (< 2.3 SD from the geometric mean) and TSH levels (1.0 μU) are combined, the number of recalled subjects falls to 1.1%.[10] Further improvement of specificity is, at present, considered unlikely without sacrifice of sensitivity in the screening program. A protocol to maintain maximum specificity and sensitivity has been developed at one center with extensive experience[10] (see Appendix).

Sensitivity

False-negative test results will occur in any screening program. The lowest possible frequency of such results (highest sensitivity) at a reasonable cost should be the most desired objective of the program.

The frequency of false-negative tests results ("normal" blood T_4 value with deficient thyroid gland activity) will be determined by the level of the cutoff value which defines a "low" T_4 concentration. This value will vary from day to day in large testing programs, and this variance should be taken into consideration in designing T_4 screening programs.

Screening for congenital hypothyroidism either by the T_4 or TSH assay alone is not advised.[5] Both tests must be available for an effective program.

Cost of Testing and Screening

The cost of the T_4 test on a filter paper blood sample or a cord blood sample is about 60 cents per test, and the TSH test is currently about $1.50 per test (1976 U.S. dollar value).[3] These relative costs may vary in other countries. The cost for screening (versus testing) will be higher because of the need for a program to maintain the process of screening, which includes several components (sample collection, laboratory analysis, record keeping, follow-up of patients, repeated testing, diagnosis, counseling, and treatment). De novo screening for T_4 deficiency will be an expensive undertaking for any community; however, for communities with existing screening structures, the added cost of T_4 screening is marginal.

STRUCTURE AND PROCESS OF T_4 SCREENING

The process of T_4 screening demands a high standard of technical competence. Validation of new programs will be extremely important if the pitfalls experienced with PKU screening are not to be repeated with the expansion of T_4 screening. The occasional use of the commercial T_4 tests now being offered—at ten times the present cost for mass T_4 screening tests—does not offer the

pediatrician or his local laboratory the essential, statistical resource required for interpretation of the T_4 test in newborn infants or the mandatory backup testing with a TSH assay.

Genetic (or metabolic) screening in the newborn infant is a process that requires an integrated structure.[1,2,12] The rationale for T_4 screening is to permit early medical intervention through the process of early diagnosis of congenital hypothyroidism. To fulfill this objective, the T_4 screening program must encompass four basic subobjectives: (1) testing, (2) patient retrieval, (3) diagnosis, and (4) follow-up (and counseling and treatment). The process by which each of these objectives is attained requires an appropriate structure.

Testing

The pediatrician must be reassured that specificity and sensitivity of T_4 testing are satisfactory. Analysis of the experience with PKU screening[2] reveals that specificity and sensitivity are maximized when testing is centralized and carefully standardized in a well-designed regional program.

The time elapsed at room temperature between collection of the sample and analysis in the laboratory can influence specificity of T_4 screening[6]; long delays cause a decrease of T_4 concentration in blood spots. A low compliance rate with sample collection in the nursery is also undesirable because this can decrease sensitivity for the program.

An efficient testing structure can be achieved by a working regional advisory committee, as in the Quebec experience,[12] or through an advisory commission, as in the Maryland experience.[2]

Patient Retrieval

Rapid diagnosis and treatment are considered essential to minimize the harm of congenital hypothyroidism. A presumptive positive screening test is a signal to retrieve the patient quickly for diagnostic studies. Any delay in performance of the screening test and any further delay in patient retrieval postpones diagnosis and treatment. Analysis of the experience with PKU screening[2] revealed that too much time elapsed in many programs between birth and retrieval of the patient and initiation of follow-up investigation. Pediatricians should insist that follow-up procedures are efficient and available. In one program[12] now performing mass T_4 screening on more than 90,000 infants per year, the program was permitted by the regional medical society to contact the patient directly at the time the physician is notified. Patient retrieval is efficient and elapsed time was shortened under these conditions. This "unorthodox" approach to patients can be achieved without harmful anxiety when the community is broadly informed about the program and follow-up is done with care for the concerns of the patient.

Diagnosis

Prognosis and management are dependent on diagnosis. A positive T_4 test (low blood T_4 concentration) is not equivalent to a diagnosis of congenital hypothyroidism. Among the 114 patients with positive screening tests reported in the pilot programs,[2] follow-up investigation revealed several diagnoses, including TBG deficiency (a harmless variant constituting 31.6% of diagnoses), pituitary deficiency (6.5%), and dyshormonogenesis (8.6%). Prognosis is different for each of these conditions. Additional diagnoses may emerge in future programs, including "new" disorders not currently recognized. The pediatrician should be reassured that the regional T_4 screening program includes a competent endocrinologist. Referral of the patient with a presumptive positive test for consultation is strongly recommended, unless the physician is personally familiar with all aspects of the differential diagnosis.

Follow-up

The rationale for screening for congenital hypothyroidism in the newborn infant is to permit early medical intervention, that is, treatment with thyroxine. Prognosis and outcome will be related not only to diagnosis but also to the age at onset of treatment and the effectiveness of therapy. It is not known yet whether early treatment of congenital hypothyroidism (primary or secondary or the various forms of hormone dysgenesis) can overcome completely the effect of hormone deficiency up to the time of diagnosis. This is why mass T_4 testing should be promoted within the context of an integrated screening program with facilities and support for long-term follow-up and evaluation.

ROLE OF THE PEDIATRICIAN

The pediatrician should be an advocate of well-designed screening programs for congenital hypothyroidism, and he should recognize that T_4 testing is different from screening for congenital hypothyroidism. T_4 testing is only one component of a screening program. The pediatrician should advocate the establishment of a regional advisory committee to ensure that testing is performed

with due recognition of the problems in maintaining high specificity and sensitivity. Integration of the resources for retrieval, diagnosis, treatment, and follow-up should be attempted. The pediatrician is an ideal advocate to advise the community of the rationale for this type of screening in newborn infants. Parents deserve to know in advance that the test is being done and why.

RECOMMENDATIONS

The opportunity to establish newborn infant screening programs for the early detection of congenital T_4 deficiency is an exciting development. It is an opportunity to eliminate a serious traditional problem in pediatrics that can be distressing both to the patient who, if not detected early, may not benefit from treatment, and to the physician who, regrettably, makes a late diagnosis. One purpose of this statement is to stress that T_4 screening is more than testing newborn infants for low blood T_4 levels. Testing is no panacea unless it is done with extreme care. The effectiveness of testing will be diminished unless there is a comprehensive program to accommodate the separate processes of testing, patient retrieval, diagnosis, and follow-up.

The Committee offers the following recommendations.

1. Testing programs designed to identify a low blood T_4 concentration in newborn infants should validate the T_4 radioimmunoassay before proceeding beyond the pilot stage. Thereafter, the testing process should be rigorously controlled.

2. Heel prick blood collected on filter paper at the time of discharge from the nursery is the preferred sample. A statistical definition of the normal T_4 value is essential to define the "low" value. A large volume of samples and a central testing laboratory will enhance specificity of the test.

3. Backup testing with TSH radioimmunoassay is essential to improve specificity of T_4 screening. The TSH assay should be validated. The program should be designed so TSH testing, when indicated, is done on the same sample with the low T_4 concentration. A protocol for repeated testing and callback of patients should be defined.

4. There should be efficient delivery of samples from the nurseries to the testing laboratory and an effective system for retrieval of subjects with presumptive positive test results. The elapsed time between birth and confirmatory testing for primary congenital hypothyroidism should not exceed 3½ weeks.

5. Diagnostic facilities should be available to investigate the patient with a presumptive positive test. A low T_4 concentration in blood may indicate primary or secondary congenital hypothyroidism, various forms of hormone dysgenesis, or serum TBG deficiency; other diagnoses may also be discovered. Prognosis and management will vary with the diagnosis.

6. Therapy by 1 month of age should be the major objective in any program screening for congenital hypothyroidism. Monitoring of treatment and evaluation of outcome should both be supported by the program.

7. A regional advisory committee is recommended to initiate a complete screening program and educate the community served by the program.

8. The pediatrician is a welcome advocate and participant at all levels of the program.

REFERENCES

1. Task Force on Genetic Screening: The pediatrician and genetic screening (every pediatrician a geneticist). *Pediatrics* 58:737, 1976.
2. National Academy of Sciences: Genetic Screening: Programs, Principles and Research. Washington, DC, National Academy of Sciences, 1975.
3. Newborn Committee of the American Thyroid Association: Recommendations for screening programs for congenital hypothyroidism. J Pediatr 89:692, 1976.
4. Klein AH, Meltzer S, Kenny FM: Improved prognosis in congenital hypothyroidism treated before age three months. J Pediatr 81:912, 1972.
5. Newborn Committee of the American Thyroid Association: Minutes of September 16, 1976, meeting. Unpublished manuscript.
6. Dussault JH, Coulombe P, Laberge C, et al: Preliminary report on a mass screening program for neonatal hypothyroidism. J Pediatr 86:670, 1975.
7. Larsen PR, Broskin K: Thyroxine (T_4) immunoassay using filter paper blood samples for screening of neonates for hypothyroidism. Pediatr Res 9:604, 1975.
8. Dussault JH, Parlow A, Letarte J, et al: TSH measurements from blood spots on filter paper: A confirmatory screening test for neonatal hypothyroidism. J Pediatr 89:550, 1976.
9. Larsen PR, Merker A, Parlow AF: Immunoassay of human TSH using dried blood samples. J Clin Endocrinol Metab 42:987, 1976.
10. Dussault JH, Morissette J, Letarte J, et al: Follow-up approach for a screening program for neonatal hypothyroidism. Unpublished manuscript.
11. Dussault JH, Morisette J, Fiset P, et al: Factors influencing results for thyroxine concentration in blood as measured in paper filter spots in a screening program for neonatal hypothyroidism. Clin Chem 22:1392, 1976.
12. Scriver CR, Clow CL, Laberge C: Genetic screening and allied services: Structure, process and objectives, in Raine DN (ed): Medical-Social Management of Inherited Metabolic Disease. Liverpool, England, M and S Publisher, to be published.

Screening for Congenital Metabolic Disorders in the Newborn Infant: Congenital Deficiency of Thyroid Hormone and Hyperphenylalaninemia

Committee on Genetics

Charles R. Scriver, M.D., Chairman; Murray Feingold, M.D.; Peter Mamunes, M.D.; *and* Henry L. Nadler, M.D.

Consultants: Barton Childs, M.D.; Jean H. Dussault, M.D.; Neil A. Holtzman, M.D.; Parvin Justice, Ph.D.; *and* Rueben Matalon, M.D.

The Committee on Genetics of the American Academy of Pediatrics was formed in 1976. The initial reports from the Committee are published in this supplement to *Pediatrics:* one on guidelines for screening the newborn infant for hyperphenylalaninemia (including phenylketonuria [PKU]) and the other on screening for congenital hypothyroidism.

The first statement describes guidelines for screening for thyroid hormone deficiency in newborn infants: it concerns a traditional problem in pediatrics, the prevention of cretinism. A statement on "T_4 screening" has already been issued by the American Thyroid Association.[1] Why is there need for another (and longer) statement from the Academy? The Task Force on Genetic Screening recommended a special review of T_4 screening, and that recommendation has been acted on quickly in the hope that most of the mistakes made in PKU screening will not be repeated in T_4 screening. The American Thyroid Association statement adequately describes the status of testing for T_4 deficiency; it does not cover other essential components of an effective screening program, namely, provision for serving patient retrieval, diagnosis, and treatment.[2] The Committee urges pediatricians and endocrinologists who elect to push ahead with T_4 testing to pause and examine the many issues of mass newborn infant screening before they act too hastily, perhaps to the detriment of their patients and newborn infant screening programs.

Dr. Jean Dussault served as consultant to the Committee when it examined T_4 screening; his personal experience extends to ¼ million screened subjects and emanates from a model program which has largely avoided many pitfalls of newborn infant screening. After reviewing that experience and examining it with the existing problems of PKU screening in mind,[2] the Committee could not recommend universal (mass) T_4 screening for a region in the absence of an advisory committee and an integrated screening program with supporting services.

The statement on screening for hyperphenylalaninemia was prepared by Dr. Neil A. Holtzman; it is intended to help pediatricians and their associates avoid the pitfalls surrounding newborn screening, which are delineated in the report from the National Academy of Sciences on Genetic Screening.[2] Screening for hyperphenylalaninemia is still evolving as an effective public health activity. For example, a newly recognized form of PKU caused by dihydropteridine reductase deficiency was discovered long after screening programs for neonatal hyperphenylalaninemia were well instituted. It is now essential to distinguish this variant from other causes of hyperphenylalaninemia for purposes of prognosis, treatment, and counseling; this imposes new requirements for backup services on the screening programs. The need for a regional commission or an advisory committee[2-4] to guide the development of new resources and to evaluate the performance of existing services is one of the lessons learned from past experience with PKU screening.[3]

This screening supplement does not consider screening for other congenital metabolic disorders which may be of interest to pediatricians, e.g., galactosemia, cystic fibrosis, and maple syrup urine disease. The principal reason for not making additional statements now is our belief that the regional advisory committees or commissions can make these decisions about implementation of "add-on" screening tests. The capabilities for the region will depend on the organization of the existing screening program. If a regional commission does not exist, the committee urges those responsible for the screening programs to familiarize themselves with the concept[2-4] and to act accordingly.

REFERENCES

1. Newborn Committee of the American Thyroid Association: Recommendations for screening programs for congenital hypothyroidism. J Pediatr 89:692, 1976.
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ACKNOWLEDGMENT

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Screening for Congenital Deficiency of Thyroid Hormone

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Congenital thyroid hormone deficiency is a prime example of a condition whose early diagnosis, as well as the opportunity for effective treatment, can be missed. The following report examines both the practice of newborn infant screening for early diagnosis of congenital thyroid hormone (T_4) deficiency and the relation of that activity to the principles of metabolic (and genetic) screening.[2] The reader is also referred to a parallel statement prepared by a committee of the American Thyroid Association.[3]

BACKGROUND INFORMATION

There is limited placental transport of thyrotropin (TSH) and the thyroid hormones 3,5,3'-triiodothyronine (T_3) and thyroxine (T_4). Serum T_4 concentration in the newborn infant will be diminished when there is congenital deficiency of thyroid tissue, impaired activity of one of the enzymes involved in thyroid hormone biosynthesis (T_4 hormone dysgenesis), deficient serum T_4 binding globulin (TBG), or deficient stimulation of thyroid (by TSH) or pituitary (by thyrotropin releasing hormone [TRH]). Primary congenital hypothyroidism (cretinism) is associated with a high frequency of mental retardation; cretinism accounts for about 1% to 2% of admissions to institutions for the mentally retarded. Only half of the patients with cretinism achieve IQs above 90 if diagnosis and treatment are delayed until 3 to 6 months of age, but 75% of patients achieve this outcome when clinical diagnosis is made and treatment begins before 3 months of age.[4] It has yet to be determined whether diagnosis and treatment within the first month of life can further improve the outcome.

An accurate radioimmunoassay system is available to measure T_4 concentration in body fluids; a corresponding assay is also available to measure TSH in body fluids. Accordingly, newborn infant screening for congenital hypothyroidism is now possible. The combined application of the T_4 and TSH assay facilitates newborn infant screening and enhances specificity and sensitivity of the process. (Specificity and sensitivity have precise meanings in screening terminology. *Specificity* is the ability of the screening test to exclude normal subjects from false detections. *Sensitivity* is the ability of the screening test to detect subjects with the abnormality.) The objective of T_4 screening in newborn infants is to obtain early diagnosis and initiate treatment at the incipient stage of hypothyroidism.

Many infants (in fact, 425,000) have already been screened for T_4 deficiency in five pilot programs. (The five programs were carried out in Quebec, 250,000 infants; New England, 70,000; Oregon, 64,000; Pittsburgh, 25,000; and Toronto, 16,000. These data are valid up to September 1976.[5]) Among these, 72 infants (or 1 in 5,900 live births) were confirmed to have primary or secondary congenital hypothyroidism and 6 others have inherited defects in the biosynthesis of T_4 (dyshormonogenesis). However, at least 36 additional infants (31.6%) have TBG deficiency as the cause for their positive T_4 screening test results. The total number of infants with a diagnosed cause for decreased serum T_4 concentration is 114 in the 425,000 tested in these pilot programs, of which 68.4% required specific treatment. Only two patients with congenital hypothyroidism have apparently been missed in these screening programs: one infant escaped diagnosis because he was not actually screened (apparent sensitivity = 78/80 for the screening programs); the other was missed by the test (apparent sensitivity = 78/79 for the test). This is an excellent, effective, early "track record" for a new form of mass screening of newborn infants; the record indicates a requirement for an effective screening program and a reliable test.

T_4 SCREENING: DETAILS

The technical aspects of T_4 testing and screening are critical for its success. Attention to details, both for the test and the program, accounts for the acceptable sensitivity of the initial pilot programs.

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Specificity

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pediatrician or his local laboratory the essential, statistical resource required for interpretation of the T_4 test in newborn infants or the mandatory backup testing with a TSH assay.

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RECOMMENDATIONS

The opportunity to establish newborn infant screening programs for the early detection of congenital T_4 deficiency is an exciting development. It is an opportunity to eliminate a serious traditional problem in pediatrics that can be distressing both to the patient who, if not detected early, may not benefit from treatment, and to the physician who, regrettably, makes a late diagnosis. One purpose of this statement is to stress that T_4 screening is more than testing newborn infants for low blood T_4 levels. Testing is no panacea unless it is done with extreme care. The effectiveness of testing will be diminished unless there is a comprehensive program to accommodate the separate processes of testing, patient retrieval, diagnosis, and follow-up.

The Committee offers the following recommendations.

1. Testing programs designed to identify a low blood T_4 concentration in newborn infants should validate the T_4 radioimmunoassay before proceeding beyond the pilot stage. Thereafter, the testing process should be rigorously controlled.

2. Heel prick blood collected on filter paper at the time of discharge from the nursery is the preferred sample. A statistical definition of the normal T_4 value is essential to define the "low" value. A large volume of samples and a central testing laboratory will enhance specificity of the test.

3. Backup testing with TSH radioimmunoassay is essential to improve specificity of T_4 screening. The TSH assay should be validated. The program should be designed so TSH testing, when indicated, is done on the same sample with the low T_4 concentration. A protocol for repeated testing and callback of patients should be defined.

4. There should be efficient delivery of samples from the nurseries to the testing laboratory and an effective system for retrieval of subjects with presumptive positive test results. The elapsed time between birth and confirmatory testing for primary congenital hypothyroidism should not exceed 3½ weeks.

5. Diagnostic facilities should be available to investigate the patient with a presumptive positive test. A low T_4 concentration in blood may indicate primary or secondary congenital hypothyroidism, various forms of hormone dysgenesis, or serum TBG deficiency; other diagnoses may also be discovered. Prognosis and management will vary with the diagnosis.

6. Therapy by 1 month of age should be the major objective in any program screening for congenital hypothyroidism. Monitoring of treatment and evaluation of outcome should both be supported by the program.

7. A regional advisory committee is recommended to initiate a complete screening program and educate the community served by the program.

8. The pediatrician is a welcome advocate and participant at all levels of the program.

REFERENCES

1. Task Force on Genetic Screening: The pediatrician and genetic screening (every pediatrician a geneticist). *Pediatrics* 58:757, 1976.
2. National Academy of Sciences: Genetic Screening: Programs, Principles and Research. Washington, DC, National Academy of Sciences, 1975.
3. Newborn Committee of the American Thyroid Association: Recommendations for screening programs for congenital hypothyroidism. J Pediatr 89:692, 1976.
4. Klein AH, Meltzer S, Kenny FM: Improved prognosis in congenital hypothyroidism treated before age three months. J Pediatr 81:912, 1972.
5. Newborn Committee of the American Thyroid Association: Minutes of September 16, 1976, meeting. Unpublished manuscript.
6. Dussault JH, Coulombe P, Laberge C, et al: Preliminary report on a mass screening program for neonatal hypothyroidism. J Pediatr 86:670, 1975.
7. Larsen PR, Broskin K: Thyroxine (T_4) immunoassay using filter paper blood samples for screening of neonates for hypothyroidism. Pediatr Res 9:604, 1975.
8. Dussault JH, Parlow A, Letarte J, et al: TSH measurements from blood spots on filter paper: A confirmatory screening test for neonatal hypothyroidism. J Pediatr 89:550, 1976.
9. Larsen PR, Merker A, Parlow AF: Immunoassay of human TSH using dried blood samples. J Clin Endocrinol Metab 42:987, 1976.
10. Dussault JH, Morissette J, Letarte J, et al: Follow-up approach for a screening program for neonatal hypothyroidism. Unpublished manuscript.
11. Dussault JH, Morisette J, Fiset P, et al: Factors influencing results for thyroxine concentration in blood as measured in paper filter spots in a screening program for neonatal hypothyroidism. Clin Chem 22:1392, 1976.
12. Scriver CR, Clow CL, Laberge C: Genetic screening and allied services: Structure, process and objective. in Raine DN (ed): Medical-Social Management of Inherited Metabolic Disease. Liverpool, England, M and S Publisher, to be published.

PEDIATRICS • VOLUME 60 • NUMBER 3 • SUPPLEMENT

Screening for Congenital Metabolic Disorders in the Newborn Infant: Congenital Deficiency of Thyroid Hormone and Hyperphenylalaninemia

Committee on Genetics

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Consultants: Barton Childs, M.D.; Jean H. Dussault, M.D.; Neil A. Holtzman, M.D.; Parvin Justice, Ph.D.; *and* Rueben Matalon, M.D.

The Committee on Genetics of the American Academy of Pediatrics was formed in 1976. The initial reports from the Committee are published in this supplement to *Pediatrics*: one on guidelines for screening the newborn infant for hyperphenylalaninemia (including phenylketonuria [PKU]) and the other on screening for congenital hypothyroidism.

The first statement describes guidelines for screening for thyroid hormone deficiency in newborn infants; it concerns a traditional problem in pediatrics, the prevention of cretinism. A statement on "T_4 screening" has already been issued by the American Thyroid Association.[1] Why is there need for another (and longer) statement from the Academy? The Task Force on Genetic Screening recommended a special review of T_4 screening, and that recommendation has been acted on quickly, in the hope that most of the mistakes made in PKU screening will not be repeated in T_4 screening. The American Thyroid Association statement adequately describes the status of testing for T_4 deficiency; it does not cover other essential components of an effective screening program, namely, provision for serving patient retrieval, diagnosis, and treatment. The Committee urges pediatricians and endocrinologists who elect to push ahead with T_4 testing to pause and examine the many issues of mass newborn infant screening before they act too hastily, perhaps to the detriment of their patients and newborn infant screening programs.

Dr. Jean Dussault served as consultant to the Committee when it examined T_4 screening; his personal experience extends to ¼ million screened subjects and emanates from a model program which has largely avoided many pitfalls of newborn infant screening. After reviewing that experience and examining it with the existing problems of PKU screening in mind,[2] the Committee could not recommend universal (mass) T_4 screening for a region in the absence of an advisory committee and an integrated screening program with supporting services.

The statement on screening for hyperphenylalaninemia was prepared by Dr. Neil A. Holtzman; it is intended to help pediatricians and their associates avoid the pitfalls surrounding newborn screening, which are delineated in the report from the National Academy of Sciences on Genetic Screening.[2] Screening for hyperphenylalaninemia is still evolving as an effective public health activity. For example, a newly recognized form of PKU caused by dihydropteridine reductase deficiency was discovered long after screening programs for neonatal hyperphenylalaninemia were well instituted. It is now essential to distinguish this variant from other causes of hyperphenylalaninemia for purposes of prognosis, treatment, and counseling; this imposes new requirements for backup services on the screening programs. The need for a regional commission or an advisory committee[2,3] to guide the development of new resources and to evaluate the performance of existing services is one of the lessons learned from past experience with PKU screening.[3]

This screening supplement does not consider screening for other congenital metabolic disorders which may be of interest to pediatricians, e.g., galactosemia, cystic fibrosis, and maple syrup urine disease. The principal reason for not making additional statements now is our belief that the regional advisory committees or commissions can make these decisions about implementation of "add-on" screening tests. The capabilities for the region will depend on the organization of the existing screening program. If a regional commission does not exist, the committee urges those responsible for the screening programs to familiarize themselves with the concept[2,3] and to act accordingly.

REFERENCES

1. Newborn Committee of the American Thyroid Association: Recommendations for screening programs for congenital hypothyroidism. J Pediatr 89:692, 1976.
2. National Academy of Sciences: Genetic Screening: Programs, Principles and Research. Washington, DC, National Academy of Sciences, 1975.
3. Task Force on Genetic Screening: The pediatrician and genetic screening (every pediatrician a geneticist). *Pediatrics* 58:757, 1976.

ACKNOWLEDGMENT

The Committee acknowledges the advice and assistance of Dr. Reuben Matalon, Dr. Parvin Justice, and Dr. Jean Lockhart, Director, Department of Committees of the American Academy of Pediatrics.

Screening for Congenital Deficiency of Thyroid Hormone

The Task Force on Genetic Screening was not able to discuss details of the various forms of genetic and metabolic screening.[1] A Committee on Genetics was formed to examine these and other issues relating to congenital disease and medical genetics. The following statement is one of the Committee's reports.

Congenital thyroid hormone deficiency is a prime example of a condition whose early diagnosis, as well as the opportunity for effective treatment, can be missed. The following report examines both the practice of newborn infant screening for early diagnosis of congenital thyroid hormone (T_4) deficiency and the relation of that activity to the principles of metabolic (and genetic) screening.[2] The reader is also referred to a parallel statement prepared by a committee of the American Thyroid Association.[3]

BACKGROUND INFORMATION

There is limited placental transport of thyrotropin (TSH) and the thyroid hormones 3,5,3'-triiodothyronine (T_3) and thyroxine (T_4). Serum T_4 concentration in the newborn infant will be diminished when there is congenital deficiency of thyroid tissue, impaired activity of one of the enzymes involved in thyroid hormone biosynthesis (T_4 hormone dysgenesis), deficient serum T_4 binding globulin (TBG), or deficient stimulation of thyroid (by TSH) or pituitary (by thyrotropin releasing hormone [TRH]). Primary congenital hypothyroidism (cretinism) is associated with a high frequency of mental retardation; cretinism accounts for about 1% to 2% of admissions to institutions for the mentally retarded. Only half of the patients with cretinism achieve IQs above 90 if diagnosis and treatment are delayed until 3 to 6 months of age, but 75% of patients achieve this outcome when clinical diagnosis is made and treatment begins before 3 months of age.[4] It has yet to be determined whether diagnosis and treatment within the first month of life can further improve the outcome.

An accurate radioimmunoassay system is available to measure T_4 concentration in body fluids; a corresponding assay is also available to measure TSH in body fluids. Accordingly, newborn infant screening for congenital hypothyroidism is now possible. The combined application of the T_4 and TSH assay facilitates newborn infant screening and enhances specificity and sensitivity of the process. (Specificity and sensitivity have precise meanings in screening terminology. *Specificity* is the ability of the screening test to exclude normal subjects from false detections. *Sensitivity* is the ability of the screening test to detect subjects with the abnormality.) The objective of T_4 screening in newborn infants is to obtain early diagnosis and initiate treatment at the incipient stage of hypothyroidism.

Many infants (in fact, 425,000) have already been screened for T_4 deficiency in five pilot programs. (The five programs were carried out in Quebec, 250,000 infants; New England, 70,000; Oregon, 64,000; Pittsburgh, 25,000; and Toronto, 16,000. These data are valid up to September 1976.[5]) Among these, 72 infants (or 1 in 5,900 live births) were confirmed to have primary or secondary congenital hypothyroidism and 6 others have inherited defects in the biosynthesis of T_4 (dyshormonogenesis). However, at least 36 additional infants (31.6%) have TBG deficiency as the cause for their positive T_4 screening test results. The total number of infants with a diagnosed cause for decreased serum T_4 concentration is 114 in the 425,000 tested in these pilot programs, of which 68.4% required specific treatment. Only two patients with congenital hypothyroidism have apparently been missed in these screening programs: one infant escaped diagnosis because he was not actually screened (apparent sensitivity = 78/80 for the screening programs); the other was missed by the test (apparent sensitivity = 78/79 for the test). This is an excellent, effective, early "track record" for a new form of mass screening of newborn infants; the record indicates a requirement for an effective screening program and a reliable test.

T_4 SCREENING: DETAILS

The technical aspects of T_4 testing and screening are critical for its success. Attention to details, both for the test and the program, accounts for the acceptable sensitivity of the initial pilot programs.

Tests

The T_4 radioimmunoassay can be applied either to dried blood spots on filter paper (Schleicher and Schull, No. 903)—collected from a heel prick or from cord blood—or to serum. One of the two recommended assays[6,7] should be used.

The TSH radioimmunoassay[8,9] can also be done on the filter paper blood specimen or on serum. Specificity of screening is augmented and economic costs are reduced when the TSH assay is applied to the same sample evincing a low T_4 level.

Measurement of reverse T_3 in blood or serum is unlikely to be a useful adjunct for newborn infant screening.[5]

The use of heel prick blood obtained at discharge from the nursery is recommended in preference to cord blood samples; specificity of the T_4 and TSH tests is better on heel prick blood.[3,5]

Specificity

False-positive test results (i.e., low T_4 levels without deficient gland activity or TBG deficiency) will occur. The lowest possible frequency of such results (highest specificity) is an essential objective of an effective T_4 screening program. Experience indicates[10] that 1.84% of filter-paper samples yield a "low" T_4 concentration (positive test). A low value by the assay applied to filter-paper, heel-blood samples is defined as a value less than 2.3 SD from the geometric mean for the day,[10] uncorrected for the weight of the infant.[11] Such precision in the cutoff level for delineation of a "low" T_4 concentration can be obtained only in a laboratory processing many samples daily under rigorously standardized conditions. The majority (98.4%) of these "positive" test results are false-positive.[10]

Attention to the birth weight of the infant permits a corrective factor to be applied, which reduces the frequency of false-positive T_4 test results by 0.15%.[11] The age of the infant does not influence the T_4 test result. A further reduction in the frequency of false-positive test results follows the application of TSH assay to the 1.84% of samples with a low T_4 value. A TSH concentration greater than 1.0 μU on filter-paper spots of heel blood indicates a "positive" test. When T_4 values (< 2.3 SD from the geometric mean) and TSH levels (1.0 μU) are combined, the number of recalled subjects falls to 1.1%.[10] Further improvement of specificity is, at present, considered unlikely without sacrifice of sensitivity in the screening program. A protocol to maintain maximum specificity and sensitivity has been developed at one center with extensive experience[10] (see Appendix).

Sensitivity

False-negative test results will occur in any screening program. The lowest possible frequency of such results (highest sensitivity) at a reasonable cost should be the most desired objective of the program.

The frequency of false-negative tests results ("normal" blood T_4 value with deficient thyroid gland activity) will be determined by the level of the cutoff value which defines a "low" T_4 concentration. This value will vary from day to day in large testing programs, and this variance should be taken into consideration in designing T_4 screening programs.

Screening for congenital hypothyroidism either by the T_4 or TSH assay alone is not advised.[5] Both tests must be available for an effective program.

Cost of Testing and Screening

The cost of the T_4 test on a filter paper blood sample or a cord blood sample is about 60 cents per test, and the TSH test is currently about $1.50 per test (1976 U.S. dollar value).[3] These relative costs may vary in other countries. The cost for screening (versus testing) will be higher because of the need for a program to maintain the process of screening, which includes several components (sample collection, laboratory analysis, record keeping, follow-up of patients, repeated testing, diagnosis, counseling, and treatment). De novo screening for T_4 deficiency will be an expensive undertaking for any community; however, for communities with existing screening structures, the added cost of T_4 screening is marginal.

STRUCTURE AND PROCESS OF T_4 SCREENING

The process of T_4 screening demands a high standard of technical competence. Validation of new programs will be extremely important if the pitfalls experienced with PKU screening are not to be repeated with the expansion of T_4 screening. The occasional use of the commercial T_4 tests now being offered—at ten times the present cost for mass T_4 screening tests—does not offer the

pediatrician or his local laboratory the essential, statistical resource required for interpretation of the T_4 test in newborn infants or the mandatory backup testing with a TSH assay.

Genetic (or metabolic) screening in the newborn infant is a process that requires an integrated structure.[1,2,12] The rationale for T_4 screening is to permit early medical intervention through the process of early diagnosis of congenital hypothyroidism. To fulfill this objective, the T_4 screening program must encompass four basic subobjectives: (1) testing, (2) patient retrieval, (3) diagnosis, and (4) follow-up (and counseling and treatment). The process by which each of these objectives is attained requires an appropriate structure.

Testing

The pediatrician must be reassured that specificity and sensitivity of T_4 testing are satisfactory. Analysis of the experience with PKU screening[2] reveals that specificity and sensitivity are maximized when testing is centralized and carefully standardized in a well-designed regional program.

The time elapsed at room temperature between collection of the sample and analysis in the laboratory can influence specificity of T_4 screening[6]; long delays cause a decrease of T_4 concentration in blood spots. A low compliance rate with sample collection in the nursery is also undesirable because this can decrease sensitivity for the program.

An efficient testing structure can be achieved by a working regional advisory committee, as in the Quebec experience,[12] or through an advisory commission, as in the Maryland experience.[2]

Patient Retrieval

Rapid diagnosis and treatment are considered essential to minimize the harm of congenital hypothyroidism. A presumptive positive screening test is a signal to retrieve the patient quickly for diagnostic studies. Any delay in performance of the screening test and any further delay in patient retrieval postpones diagnosis and treatment. Analysis of the experience with PKU screening[2] revealed that too much time elapsed in many programs between birth and retrieval of the patient and initiation of follow-up investigation. Pediatricians should insist that follow-up procedures are efficient and available. In one program[12] now performing mass T_4 screening on more than 90,000 infants per year, the program was permitted by the regional medical society to contact the patient directly at the time the physician is notified. Patient retrieval is efficient and elapsed time was shortened under these conditions. This "unorthodox" approach to patients can be achieved without harmful anxiety when the community is broadly informed about the program and follow-up is done with care for the concerns of the patient.

Diagnosis

Prognosis and management are dependent on diagnosis: A positive T_4 test (low blood T_4 concentration) is not equivalent to a diagnosis of congenital hypothyroidism. Among the 114 patients with positive screening tests reported in the pilot programs,[5] follow-up investigation revealed several diagnoses, including TBG deficiency (a harmless variant constituting 31.6% of diagnoses), pituitary deficiency (6.5%), and dyshormonogenesis (8.6%). Prognosis is different for each of these conditions. Additional diagnoses may emerge in future programs, including "new" disorders not currently recognized. The pediatrician should be reassured that the regional T_4 screening program includes a competent endocrinologist. Referral of the patient with a presumptive positive test for consultation is strongly recommended, unless the physician is personally familiar with all aspects of the differential diagnosis.

Follow-up

The rationale for screening for congenital hypothyroidism in the newborn infant is to permit early medical intervention, that is, treatment with thyroxine. Prognosis and outcome will be related not only to diagnosis but also to the age at onset of treatment and the effectiveness of therapy. It is not known yet whether early treatment of congenital hypothyroidism (primary or secondary or the various forms of hormone dysgenesis) can overcome completely the effect of hormone deficiency up to the time of diagnosis. This is why mass T_4 testing should be promoted within the context of an integrated screening program with facilities and support for long-term follow-up and evaluation.

ROLE OF THE PEDIATRICIAN

The pediatrician should be an advocate of well-designed screening programs for congenital hypothyroidism, and he should recognize that T_4 testing is different from screening for congenital hypothyroidism. T_4 testing is only one component of a screening program. The pediatrician should advocate the establishment of a regional advisory committee to ensure that testing is performed

with due recognition of the problems in maintaining high specificity and sensitivity. Integration of the resources for retrieval, diagnosis, treatment, and follow-up should be attempted. The pediatrician is an ideal advocate to advise the community of the rationale for this type of screening in newborn infants. Parents deserve to know in advance that the test is being done and why.

RECOMMENDATIONS

The opportunity to establish newborn infant screening programs for the early detection of congenital T_4 deficiency is an exciting development. It is an opportunity to eliminate a serious traditional problem in pediatrics that can be distressing both to the patient who, if not detected early, may not benefit from treatment, and to the physician who, regrettably, makes a late diagnosis. One purpose of this statement is to stress that T_4 screening is more than testing newborn infants for low blood T_4 levels. Testing is no panacea unless it is done with extreme care. The effectiveness of testing will be diminished unless there is a comprehensive program to accommodate the separate processes of testing, patient retrieval, diagnosis, and follow-up.

The Committee offers the following recommendations.

1. Testing programs designed to identify a low blood T_4 concentration in newborn infants should validate the T_4 radioimmunoassay before proceeding beyond the pilot stage. Thereafter, the testing process should be rigorously controlled.

2. Heel prick blood collected on filter paper at the time of discharge from the nursery is the preferred sample. A statistical definition of the normal T_4 value is essential to define the "low" value. A large volume of samples and a central testing laboratory will enhance specificity of the test.

3. Backup testing with TSH radioimmunoassay is essential to improve specificity of T_4 screening. The TSH assay should be validated. The program should be designed so TSH testing, when indicated, is done on the same sample with the low T_4 concentration. A protocol for repeated testing and callback of patients should be defined.

4. There should be efficient delivery of samples from the nurseries to the testing laboratory and an effective system for retrieval of subjects with presumptive positive test results. The elapsed time between birth and confirmatory testing for primary congenital hypothyroidism should not exceed 3½ weeks.

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6. Therapy by 1 month of age should be the major objective in any program screening for congenital hypothyroidism. Monitoring of treatment and evaluation of outcome should both be supported by the program.

7. A regional advisory committee is recommended to initiate a complete screening program and educate the community served by the program.

8. The pediatrician is a welcome advocate and participant at all levels of the program.

REFERENCES

1. Task Force on Genetic Screening: The pediatrician and genetic screening (every pediatrician a geneticist). *Pediatrics* 58:757, 1976.
2. National Academy of Sciences: Genetic Screening: Programs, Principles and Research. Washington, DC, National Academy of Sciences, 1975.
3. Newborn Committee of the American Thyroid Association: Recommendations for screening programs for congenital hypothyroidism. J Pediatr 89:692, 1976.
4. Klein AH, Meltzer S, Kenny FM: Improved prognosis in congenital hypothyroidism treated before age three months. J Pediatr 81:912, 1972.
5. Newborn Committee of the American Thyroid Association: Minutes of September 16, 1976, meeting. Unpublished manuscript.
6. Dussault JH, Coulombe P, Laberge C, et al: Preliminary report on a mass screening program for neonatal hypothyroidism. J Pediatr 86:670, 1975.
7. Larsen PR, Broskin K: Thyroxine (T_4) immunoassay using filter paper blood samples for screening of neonates for hypothyroidism. Pediatr Res 9:604, 1975.
8. Dussault JH, Parlow A, Letarte J, et al: TSH measurements from blood spots on filter paper: A confirmatory screening test for neonatal hypothyroidism. J Pediatr 89:550, 1976.
9. Larsen PR, Merker A, Parlow AF. Immunoassay of human TSH using dried blood samples. J Clin Endocrinol Metab 42:987, 1976.
10. Dussault JH, Morissette J, Letarte J, et al: Follow-up approach for a screening program for neonatal hypothyroidism. Unpublished manuscript.
11. Dussault JH, Morisette J, Fiset P, et al: Factors influencing results for thyroxine concentration in blood as measured in paper filter spots in a screening program for neonatal hypothyroidism. Clin Chem 22:1392, 1976.
12. Scriver CR, Clow CL, Laberge C: Genetic screening and allied services: Structure, process and objective, in Raine DN (ed): Medical-Social Management of Inherited Metabolic Disease. Liverpool, England, M and S Publisher, to be published.

Recommendations for screening programs for congenital hypothyroidism

Report of a Committee of The American Thyroid Association

RECENT EVIDENCE that the placental transfer of thyrotropin and thyroid hormones is markedly limited, as well as the recent availability of highly sensitive and specific radioimmunoassay systems for measurement of thyroid hormones and TSH in biologic fluids, has made newborn screening for congenital hypothyroidism feasible. During the past three years pilot screening programs have been ongoing in Quebec, Pittsburgh, and Toronto. The American Thyroid Association appointed an Ad Hoc Committee on Newborn Screening for Congenital Hypothyroidism to monitor these programs and to make recommendations regarding screening based on the accumulated results of these pilot programs. The committee and the Association have accumulated enough evidence to make preliminary recommendations which are included in the present report. This report was approved for publication by the members of The American Thyroid Association at the business meeting June 12, 1975.

Dr. Dussault and colleagues[1, 2] in Quebec adapted the T_4 radioimmunoassay system to eluates of filter paper blood spots already in use for phenylketonuria screening. Drs. Larsen and Broskin[3] have further simplified the filter paper spot T_4 method. Dr. Foley and colleagues[4] in Pittsburgh have screened cord blood using a conventional TSH radioimmunoassay system. Dr. Walfish and collaborators[5, 6] in Toronto have screened with the filter-paper-spot T_4 method at three to five days of age and with T_4 and TSH radioimmunoassay of cord blood samples. By June, 1975, approximately 100,000 infants had been screened in the Quebec program; 15 hypothyroid neonates and six infants with low thyroxine-binding globulin levels were detected. Fifteen thousand infants had been screened in Pittsburgh; four hypothyroid neonates and one infant with a low TBG level were detected. In the Toronto program 6,000 infants had been screened; two hypothyroid neonates and six infants with low TBG levels were detected. The total number of newborn infants screened approximated 121,000, and 21 infants with congenital hypothyroidism had been detected (Table I), an incidence of one in 5,760 newborn infants.

Analysis of the test results from the 21 infants with proved congenital hypothyroidism (Table II) detected by the screening programs revealed that 11 had serum T_4 values <7 μg/dl at birth or at two to four days of age; all of six infants with cord blood TSH measurements had TSH levels >50 μU/ml and five of six had values >100 μU/ml. Seven of ten infants in the Quebec study with serum TSH measurements conducted on recall between two and four weeks had TSH values in excess of 50 μU/ml. One other had a modestly elevated level (32 μU/ml). One of the remaining two infants had hypopituitarism with a low serum TSH value; the other one was euthyroid with a normal serum TSH concentration and a high serum T_3 value.

See related articles, pp. 541 to 550.

Abbreviations used
TSH: thyroid-stimulating hormone
T_4: thyroxine
TBG: thyroid-finding globulin
T_3: tri-iodothyronine

Logistical difficulties in recalling infants for retesting can be significant. In the filter paper T_4 screening programs 0.7 to 1.0% of samples require retesting, and 2.0 to 2.5% of samples require retesting when cord blood is used in the T_4 screening programs. Preliminary evidence suggests that cord blood TSH screening may miss infants with hypothyroidism secondary to TSH deficiency. Filter paper spot T_4 screening may miss infants with compensated or partial thyroid insufficiency, although the proportion of such cases is not yet clear. The effects of early thyroid hormone treatment (begun before one month of age) have yet to be defined. It is anticipated, however, that results will be at least as good as therapy begun before three months of age; 85% of such infants have IQ values >85.[7]

The cost of T_4 screening using filter paper spots or cord blood samples approximates $0.60/test. Cord blood or filter paper TSH screening costs approximately $1.50/test.

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Table I. Results of preliminary screening programs for congenital hypothyroidism

	No. of infants screened	No. of abnormal infants detected		Type of screening
		Hypothyroid	Low TBG	
Dussault et al., Quebec	100,000	15	6	Filter paper spot 2-4 days
Foley et al., Pittsburgh	15,000	4	1	Cord blood TSH
Walfish et al., Toronto	6,000	2	6	Cord blood T_4 and TSH; filter paper blood spot at 3-5 days
Totals	121,000	21	13	

Table II. T_4, T_3 and TSH measurement results in infants with hypothyroidism detected by screening programs

	Cord serum T_4 (μg/dl)		Filter paper spot T_4 (μg/dl equivalent)		Cord serum TSH		2-4 week TSH		
	<5.0	5.0-7.0	<5.0	5.0-7.0	50-100	>100	<20	20-100	>100
Quebec: Dussault et al.			11/15	4/15			2/10	3/10	5/10
Pittsburgh: Foley et al.	2/4	2/4				4/4			
Toronto: Walfish et al.		2/2			1/2	1/2		1/2	1/2

The cost of detection of each congenitally hypothyroid newborn infant by T_4 screening approximates $4,000 and by TSH screening $12,000. Assuming, conservatively, that 30% of infants with delayed diagnosis will require institutional care at $10,000 yearly for 30 years and that only 10% of infants diagnosed at birth will require such care, a screening program can save $600,000 for each ten infants detected.

On the basis of this information The American Thyroid Association recommends:

1. The establishment and expansion of preliminary screening programs for congenital hypothyroidism.

2. Combining testing for hypothyroidism with existing newborn screening programs to improve cost effectiveness and help guarantee quality control and efficient follow-up. The advantages of a regional approach to screening have been demonstrated in Quebec and this experience can serve as a model for other areas.

3. Screening for congenital hypothyroidism using a filter paper T_4 method with filter paper TSH testing of suspicious samples. This is particularly applicable where samples must be mailed to a central laboratory *or*:

4. Screening for congenital hypothyroidism using cord blood T_4 testing where samples can be processed locally. Suspicious samples should be retested using a TSH radioimmunoassay.

5. Further development of TSH measurement methods for newborn hypothyroid screening, particularly for filter paper samples. Recent studies have shown that such measurements are feasible.[3]

6. Study of screening for hypothyroidism using reverse T_3 measurements.[4] This method may be applicable to in utero screening of high-risk mothers as well as newborn screening.

7. Development of adequate pools of T_4 and TSH antisera to support widespread public screening programs for congenital hypothyroidism.

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REFERENCES

1. Newborn screening for hypothyroidism, *in* Fisher DA, and Burrow GN, editors: Perinatal thyroid physiology and disease, New York, 1975, Raven Press:
   (a) Fisher DA and Sack J: pp 197-209;
   (b) Larsen PR and Abuid J: pp 211-219;
   (c) Dussault JH, Coulombe P, and Laberge C: pp 221-229;
   (d) Foley TP Jr, Klein AH, Agustin AV and Hopwood N: pp 255-262.
   (e) Walfish PG: pp 249-254 and 263-269.
2. Dussault JH, Coulombe P, Laberge C, Letarte J, Guyda H, and Khoury K: Preliminary report on a mass screening for neonatal hypothyroidism, J PEDIATR 86:670, 1975.
3. Larsen PR, and Broskin K: Thyroxine immunoassay using filter paper blood samples for screening of neonates for hypothyroidism, Pediatr Res 9:604, 1975.
4. Klein AH, Agustin AV, and Foley TP Jr: Successful laboratory screening for congenital hypothyroidism, Lancet 1:77, 1974.
5. Walfish PG, O'Dou[illegible] J, Ulbright T, Shachter G, [illegible] Frankl A: Screening for neonatal hypothyroidism: Comparison of neonatal dried capillary blood thyroxine (T_4) to [illegible] serum T_4 and thyrotropin (TSH), Robbins J and Braverman LE, editors: Proceedings, VII International Thyroid Congress, Boston, June, 1975, Thyroid Research, Amsterdam, 1976, Excerpta medica, pp 601-605.
6. Klein A, Meltzer S, and Kenny MD: Improved prognosis in congenital hypothyroidism treated before age three months, J PEDIATR 81:912, 1972.
7. Irie M, Enomoto K, and Naruse H: Measurment of thyroid-stimulating hormone in dried blood spot, Lancet 2:1233, 1975.
8. Grajwer LA, Lam RW, Bruce VA, Parlow AF, and Fisher DA: A sensitive TSH radioimmunoassay for newborn thyroid screening, Clin Res 24:192A, 1976.
9. Chopra IJ, and Crandall BF: Thyroid hormones and thyrotropin in amniotic fluid, N Engl J Med 293:740, 1975.

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associated with the Fanconi syndrome, including cystinosis, poisoning by various chemicals, ingestion of outdated tetracycline, and malignant tumors.[251] It may also occur in the absence of any of the above factors.[388,445] Treatment with large supplements of vitamin D and perhaps phosphate may be effective in controlling the bone disease.[251]

Since the most striking biochemical changes are those present in urine, this syndrome is most readily diagnosed by urine testing. Unfortunately, most instances of the Fanconi syndrome are probably not manifest in urine during early infancy. In cystinosis, urinary abnormalities are not initially apparent until about four to six months of age.[55] However, one infant with the Fanconi syndrome but without cystinosis has been diagnosed in Massachusetts as a result of routine urine screening (Table XIII). The first urine, obtained when he was three weeks old, revealed a pattern of moderate cystine-lysinuria but did not contain an excess of glucose or protein. Another urine specimen, obtained when he was five weeks old, contained a marked generalized hyperaminoaciduria, glucosuria, and proteinuria. His father was bedridden with severe osteomalacia associated with the syndrome. At four months the infants had an increased serum alkaline phosphatase concentration.[267] Treatment with supplements of vitamin D have been instituted. Therapeutic measures initiated in infancy in this disorder may take many years to evaluate.

Rickets (Vitamin D-Dependent)

By routine urine chromatography, a 10-week-old Massachusetts infant was discovered with marked hyperaminoaciduria and slight glucosuria. Evaluation revealed the biochemical and radiographic changes of rickets. Treatment with large doses of vitamin D resulted in healing of the rickets and clearing of both the hyperaminoaciduria and glucosuria.

DISORDERS DIAGNOSED BY SCREENING
2. CARBOHYDRATE DISORDERS

Galactosemia

In terms of clinical severity during the neonatal period "classical" galactosemia may resemble MSUD or the acute "neonatal variant" form of argininosuccinic aciduria. The infant frequently develops vomiting, jaundice, hepatomegaly, and failure to thrive during the first days or weeks following the ingestion of milk.[135] If untreated, the disease may rapidly

result in death or may develop into a chronic phase characterized by cirrhosis, cataracts, and mental retardation.[136,207] An occasional infant escapes the more dramatic clinical signs during the neonatal period,[324] but it appears that almost all untreated galactosemic individuals manifest some degree of mental subnormality as they mature.[207] There is almost no activity of galactose-1-phosphate uridyl transferase (transferase), the enzyme responsible for the transfer of galactose-1-phosphate to the nucleotide, uridine diphosphoglucose.[221] This deficiency in galactose-1-phosphate utilization results in markedly increased blood and urine galactose concentrations. A diet free of lactose has been effective in reducing the biochemical and clinical severity of the disease, though the extent to which the diet may prevent mental retardation is not yet known.[137] A variant of "classical" galactosemia in which galactose metabolism seems to be present in liver though virtually absent in erythrocytes has been reported in American blacks.[356] Additional galactosemic variants in which erythrocyte transferase is deficient but in which residual activity is greater than in the "classical" galactosemic are being discovered with increasing frequency.[99a,181a,371a]

Gitzelmann has described a second form of galactosemia in which galactokinase activity is virtually absent but in which galactose-1-phosphate uridyl transferase activity is normal.[162] These patients differ clinically from "classical" galactosemics in that they have only cataracts as an abnormal finding. In particular, liver disease or mental retardation has not been present. At least six individuals with galactokinase deficiency have now been recognized.[53,162,308,326] All have had increased galactose concentrations in blood and urine. The value of a lactose-free diet in preventing the formation of cataracts in this disorder has not yet been ascertained. Recently, Gitzelmann described a third disorder of galactose metabolism, that involving deficient UDP-galactose-4-epimerase (epimerase) deficiency.[163a] This infant had a mild blood galactose increase (9 mg/100 ml) and was clinically normal.

In 1964 Guthrie introduced an *"E. coli"* test for the determination of galactose concentrations in dried blood specimens to a few laboratories who were already actively engaged in neonatal screening.[171] However, at least one laboratory (Massachusetts) had difficulty maintaining the bacterial sensitivity necessary for this test. Thus, when the specific galactose-1-phosphate uridyl transferase assay of Beutler and Baluda was developed for use on dried blood specimens,[51] many laboratories adopted this method of screening for galactosemia. This latter method has the advantage of testing specifically for the enzyme defect in "classical" galactosemia and can be used to test umbilical cord blood, but it is not useful in detecting other forms of galactosemia such as that due to

galactokinase deficiency. This "Beutler" test is also positive in certain variant conditions not associated with increased blood galactose concentrations, for example, in those who are doubly heterozygotic for the Duarte variant form of the transferase as well as for "classical" galactosemia.[395] The "Paigen" test for galactose[312] has been used successfully in several laboratories and offers certain technical advantages particularly organism stability, over the original *"E. coli"* test.

Over three million neonates have now been screened for galactosemia using one of the above testing methods (Table XV). This represents almost as many infants as have been tested for MSUD. Approximately 55% were tested by the specific "Beutler" test and most of the others were screened by the *"E. coli"* test. Currently most screening laboratories are using the "Beutler" test though the "Paigen" test is also used in Switzerland and in Massachusetts.

Fifty-eight infants with transferase-deficient forms of galactosemia have been detected (Table XV). This represents an overall incidence of about 1:65,000, a higher frequency than that of 1:100,000 predicted by Beutler as based on heterozygote detection among the general population.[50,52] However, the incidence of "classical" galactosemia as determined from newborn screening varies considerably among geographic areas, as noted in Table XVI.

There have as yet been few recorded data regarding the clinical and biochemical characteristics of infants with transferase-deficient galactosemia detected by screening. Several infants have died frequently with sepsis, before treatment could be initiated.[226,395] However, others have lived, and of these almost all are on treatment with a low-lactose or lactose-free diet.[173,181a,125]

Sudden death among neonates with "classical" galactosemia is a finding that was not generally appreciated prior to screening programs. Several of these deaths have been associated with gram-negative bacteremia, especially *E. coli*.[226,395] Whether or not galactosemia predisposes to such sepsis is not yet clear, although such predisposition may be suggested by the fact that the organisms associated with sepsis in newborn galactosemia have been lactose fermenters.[226] Nevertheless, early death has been encountered often enough to suggest that screening for galactosemia should be performed sooner than is possible when the usual blood specimen obtained from the newborn is used. Consequently, in Massachusetts the general screening program now includes the collection of dried umbilical cord blood specimens. The "Beutler" test is performed on these specimens.

Two infants with galactosemia due to galactokinase deficiency have been detected by routine neonatal screening. The first has been described

TABLE XV. Galactosemia—Results of Screening among Newborn Populations

Country	Test	Number screened	Number of transferase-deficient galactosemics detected (incidence)	Number of galactokinase-deficient infants detected (incidence)	References
Austria	*"E. coli"*	361,359	11 (1:33,000)	1 (1:360,000)	173, 424, 425
Canada	Chromatography	25,897	2 (1:13,000)	0	151
Denmark	*"E. coli"*	30,000	1 (1:30,000)	0	173, 286
France	?	10,934	2 (1:5,500)	0	55a
Germany	*"E. coli"*	375,537	9 (1:42,000)	0	55a, 173, 59a
Great Britain					
Scotland	*"E. coli"*	77,000	0	0	173, 413
Israel	Beutler	10,000	0	[a]	173, 110
New Zealand	Beutler	67,535	1 (1:68,000)	[a]	173, 437
Poland	Beutler	119,089	1 (1:119,000)	[a]	74
Sweden	*"E. coli"*	240,000	2 (1:120,000)	1 (1:240,000)	173
Switzerland	Beutler	435,665	7 (1:62,000)[c]	[a]	173, 163
	"E. coli" Paigen	259,480[c]	0	0	173, 163
United States	Beutler	1,204,423	14 (1:86,000)	[a]	415, 435a, 395, 267,
	"E. coli"	379,026	2 (1:190,000)	[a]	76, 357, 286a
	Paigen	258,018	6 (1:43,000)[c]	[a]	254b
Total		3,758,602	58 (1:65,000)	2 (1:750,000)[b]	

[a] Galactokinase deficiency cannot be detected by the "Beutler" test.
[b] Incidence calculated on basis of number of infants screened by a test other than the "Beutler" assay.
[c] Several of these infants in Switzerland and Massachusetts were detected with both the Beutler and the Paigen tests simultaneously. In Switzerland, the infants screened with the Paigen test were also screened by the Beutler assay so that the total number of newborns screened is represented by those tested by the Beutler assay.
? Indicates information could not be verified.

TABLE XVI. Ranges of Incidence Data from Phenylketonuria and Galactosemia Screening (Over 100,000 Newborns Tested)

Disorder	High		Low	
Phenylketonuria	Oregon	(1:8,000)	District of Columbia	(0:77,000)
Galactosemia	Austria	(1:33,000)	Massachusetts	(1:86,000)

in detail by Thalhammer *et al.*[126] This infant was Gypsy just as was the first family reported from Switzerland.[162] She has been treated with a galactose-restricted diet and has no signs of cataract formation. The second infant was recently discovered in Sweden,[173] but details regarding this infant are not yet available.

DISORDERS DIAGNOSED BY SCREENING
3. RED BLOOD CELL DISORDERS

Glucose-6-phosphate Dehydrogenase (G-6-PD) Deficiency

The apparent frequency of G-6-PD deficiency is as much a factor in its current prominence among disorders for which screening may be desirable as is the basic nature of the disorder itself. Among certain groups, such as American and African blacks, Filipinos, Sephardic Jews, and Sardinians, the incidence of this condition may be greater than 10%,[24] and it has been estimated that as many as 100 million individuals in the world are affected.[18] Thus, in contrast to the disorders previously discussed, genetic screening for G-6-PD deficiency would have a high yield of affected individuals.

The factor of high frequency, however, would not be enough to suggest screening for G-6-PD as a health measure were it not for the fact that the disorder may have serious clinical complications. These complications include hemolytic anemia with crises accompanied by weakness, jaundice, and black urine. The crises are usually precipitated by exposure to certain drugs such as several in the antimalarial, analgesic, sulfonamide, or nonsulfonamide antibacterial groups or by infection or exposure to fava beans.[49,313] Deaths have occurred,[49] although the crisis is usually self-limiting.[185] It is believed that the hemolysis may in some way relate to the

FROM: H. L. LEVY & J. P. KENNEDY. GENETIC SCREENING FOR INBORN ERRORS OF METABOLISM. U. S. DEPT. OF H.E.W. PUB. NO. (HSM 72-5258 (1972)

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or epidemiological rather than
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ne test to physicians who may
disorders. In some instances
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who is also a physician. Dr.
ion with the late Dr. Mary

Efron, an active clinical and basic researcher in the inborn errors of metabolism at the Massachusetts General Hospital. This type of relationship has been continued and even strengthened by those who are now in charge of the Massachusetts program and who are active at both the state laboratories and the medical center. Consequently in Massachusetts the physicians who conduct the screening program also evaluate and care for many of the patients. Thus both aspects of genetic screening can be evaluated in an integrated manner. It may be that associations such as this will lead to a reciprocal relationship between public health facilities and medical centers in many other areas of health care.

Organization of Screening

In addition to leading to lower unit costs, large screening programs are also in a better position to evaluate the technical and medical aspects of screening than small programs. Centralized facilities in Austria, Massachusetts, and Australia each perform hundreds of thousands of tests yearly. The experience gained by doing so many tests results in technical expertise. Furthermore, with the relatively large numbers of affected infants discovered in such programs, wide experience is gained in the biochemical spectrum of each disorder. Conversely, programs in which only a few hundred or even a few thousand infants per year are tested lack this necessary experience.

Ideally, genetic screening should be organized within public facilities on at least a regional basis. Thus in the United States a single laboratory could test 500,000 to a million infants a year from several states in a region. A similar organization of screening could be established in Europ across national boundaries. Evaluation and treatment centers could be established at local and state levels in cooperation with medical centers.

Cost versus Benefit

The costs of genetic screening, both tangible and intangible, are considerable, as has been noted above, and must be weighed against the resulting benefits to individuals and to society. These benefits may include those that are economic as well as those that are humanistic. In terms of economics, only PKU screening would seem to clearly meet the standards of efficiency at the present time. For instance, each year in a population of 100,000 newborns, seven could be expected to have PKU. If none received treatment and if three to four each subsequently

Mass Screening for Genetic Disease

ROBERT GUTHRIE *State University of New York, Buffalo*

Automation has already brought our screening capability to the point where the same specimen can be used to detect a number of hereditary aminoacidurias in addition to PKU. Yet application falls far behind: only six laboratories in the U. S. now do such automated multiple testing. Regionalizing the effort could close this gap – and involve practically no increase in cost over that of screening for PKU alone.

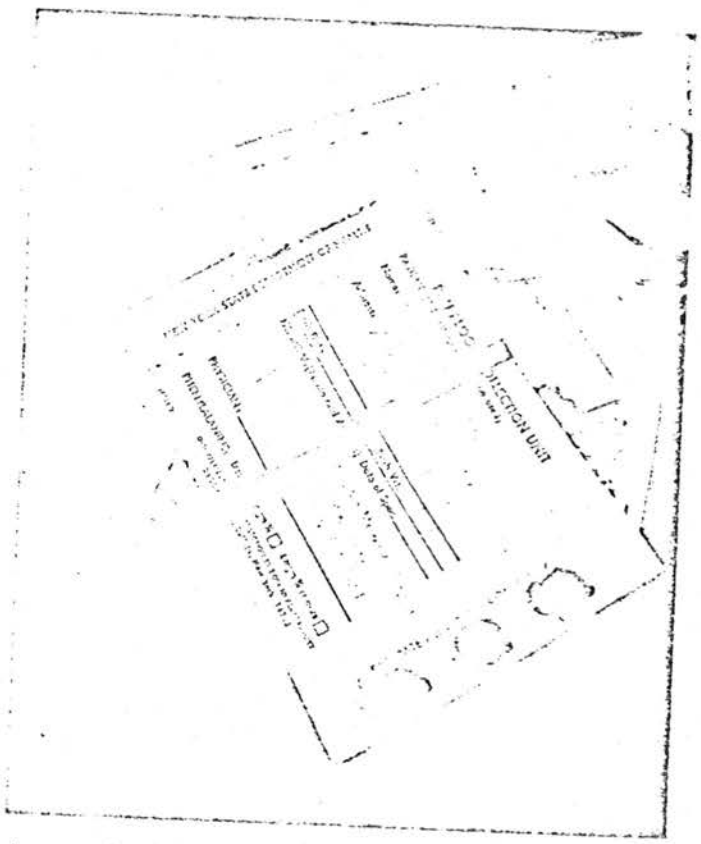
It is now some five years since mass screening of neonates for phenylketonuria became routine throughout the United States. The tests have been made legally mandatory in 43 states and are carried out voluntarily in the other seven, thereby covering an estimated 90% of the 3.5 million infants born annually in this country; similar measures are under way in at least 15 other nations. All told, these screening programs add up to perhaps the most extensive exercise in preventive medicine since the development of polio vaccine.

Given a public health effort of this magnitude, a review of the results would be appropriate in any case. But such a review seems especially desirable now, in the light of some current efforts to discontinue screening programs under the guise of a misconceived "economy." In fact, as I shall demonstrate, PKU screening has proved itself not merely a medical but also an economic success, figured in the most hard-nosed budgetary terms: the ounce of prevention that saves an expensive pound of amelioration. It is also, as we are learning, a prototype of other mass screening programs that can pay more modest, but no less real, medical and economic dividends in the prevention of genetic disease.

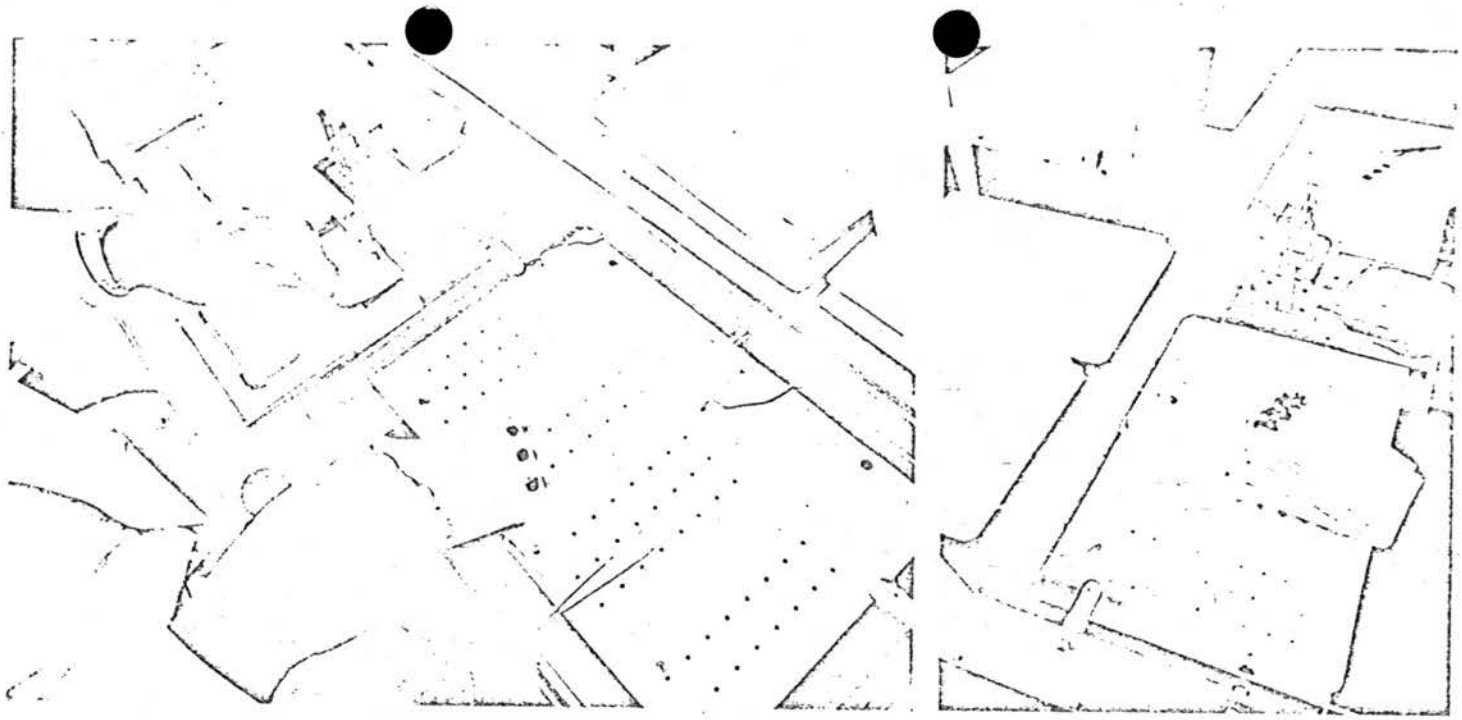
The first test for PKU was, of course, the well-known "blue-diaper" test, which depends on the reaction between ferric chloride and the phenylpyruvic acid in the urine of an affected infant. With the aid of this procedure, a number of cases of PKU were detected. These were treated by means of a low-phenylalanine diet, with results that were somewhat equivocal but encouraging. However, this test was unsuitable in many ways. First, it usually gave positive results at best no earlier than about a month after birth, owing to the delay in rise of serum levels of phenylalanine to the point where its metabolic product would show up in the urine; thus there was reason to suspect that by the time treatment could be initiated the infant might already have suffered some degree of irreversible brain damage. Then, its success as a mass screening device depended heavily on the cooperation of untrained or inexperienced individuals – parents, public health nurses, etc. – who would have only the most general notion of what to look for, since their chances of having seen another case of this rare condition were remote.

In the late 1950's, my associates and I were asked to run tests on serum phenylalanine levels to monitor the dietary treatment of two PKU patients. Dissatisfied with existing procedures, which were cumbersome and costly, we devised the bacterial inhibition test, which is neither.

This procedure employs cultures of *Bacillus subtilis* in an agar medium. Normally, this organism is capable of



Automated screening for PKU and other inborn metabolic disorders begins with the arrival by mail of blood samples like those shown above; on a recent Thursday a total of 137 arrived at the New York State health department's laboratory in Buffalo.



Filter papers containing the blood samples are placed in machine for punching (left); one dried blood spot yields four discs (as shown at far right), each of which is positioned by a suction device in a separate dimpled tray (center) for testing. Another spot is punched for trays containing agar medium (trays of this type can be seen at the technician's right). Twelve tests are made

synthesizing phenylalanine (which it requires for growth), but if the medium contains the compound β-2-thienylalanine, an analogue of phenylalanine, some essential metabolic process is blocked, so that the bacterium cannot reproduce. When a filter-paper disc impregnated with serum or blood from an affected individual is placed on the medium, however, the exogenous phenylalanine diffuses into the medium, producing a zone of growth surrounding the disc. By appropriately adjusting the concentration of the inhibitor, the test can be made sensitive over virtually the entire range of expected phenylalanine concentrations, the width of the zone of growth being proportional to the amount of phenylalanine present.

Since (as was soon determined) the serum or blood did not need to be fresh, the test could be applied on a mass basis, with samples processed in batches at central locations. There was a consequent gain in both reliability and economy, an advantage already suggested by trials with urine-impregnated filter papers. Further modifications involved using standardized discs, mechanically punched from the impregnated paper, and spores of *B. subtilis*, rather than the organism itself, for "seeding" the medium. This "instant" culture technique obviated the sterile procedures previously needed to maintain the culture and perform the test.

It is this test that has become the standard method used in nearly all PKU screening programs. It has proved itself accurate, quantitative, and reliable, as any test designed to screen for a rare disease must be. As might be expected, its widespread use has taught us a good deal about PKU itself. In most European and American populations, PKU incidence turns out to be about one case per 10,000 births, implying a gene frequency (allowing for consanguinity) of something less than one per hundred of population. Though this incidence is low, it is – significantly, I think – a good deal higher than previous estimates based on urine testing. One might note, incidentally, that both Ashkenazic Jews and (especially) Afro-Americans appear to have an unusually low incidence of PKU.

The fact that the test is carried out in the immediate postnatal period (3 to 5 days in normal infants, 5 to 8 days in prematures), in addition to making possible more timely treatment, has sharpened our awareness of the potential significance of particular phenylalanine levels. Originally, a level of 20 mg% or more was considered diagnostic, but the discriminatory level has steadily been lowered to the point where now the test is so adjusted as to pick out all infants with levels exceeding 4 mg%. A test this sensitive can be expected to turn up many "positives," and in fact we find that we can expect to retest 30 to 50 suspicious cases to turn up one actual case of PKU. Nonetheless, the extra sensitivity is justified, since it has become apparent that there is no sharp correlation between inherited lack of the enzyme phenylalanine hydroxylase (the fundamental biochemical defect in PKU) and actual serum levels of the amino acid. Of all infants with the enzyme defect, as determined by phenylalanine loading tests, some 25% maintain phenylalanine serum levels of between 8 mg% and 15 mg% on a normal diet – levels that would once have been considered benign.

Of course we cannot be certain that these infants would grow up retarded, since the only conservative (and ethical) course is to limit their phenylalanine intake as if they were "typical" PKU cases. But it is significant that

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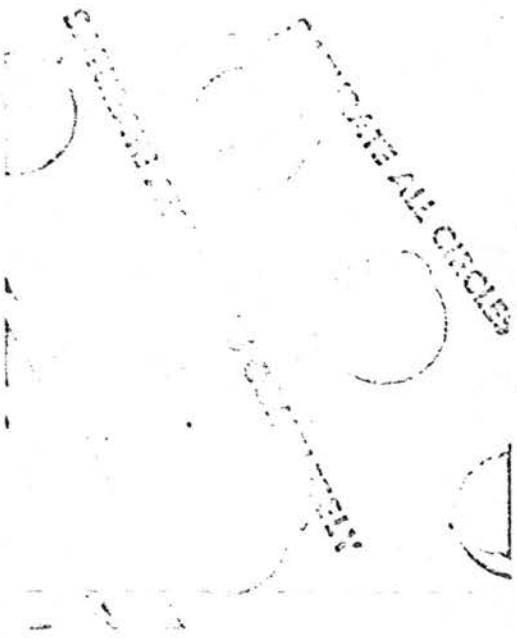


possible by the three samples. Four are routine: for phenylalanine, leucine, methionine, and tyrosine.

studies in Germany, Austria, Denmark, Scotland, and the U.S. of mentally retarded populations have turned up a significant number (25% of persons with elevated phenylalanine levels) of individuals with serum levels in this low range – levels, incidentally, at which phenylketone does *not* show up in the urine, suggesting that a more accurate term for the disease would be phenylalaninemia.

My own feeling is that infants in whom phenylalanine levels of 6 mg% or greater persist for two weeks after the initial test, and in whom the finding of phenylalaninemia is confirmed by more precise techniques such as chromatography, should be considered at least provisional PKU patients and placed immediately on a low-phenylalanine diet. This conclusion is based not merely on the general desirability of giving any disease prompt treatment but on what we know about the nature of PKU specifically. It is generally believed that most if not all the pathologic effects of phenylalaninemia derive from inhibition, by the abnormal concentrations of this amino acid, of cellular uptake of other equally essential amino acids, with resultant growth retardation. Because of its extraordinarily rapid expansion in the postnatal period, the brain is the main and perhaps the only "victim" of this growth limitation. It follows, then, that any delay in treatment beyond the minimum period necessary for a confirmed diagnosis risks brain damage; it is during the first few months of life that the brain grows most rapidly.

It is possible that in some of these marginal cases the patients may not be true PKU sufferers but may be manifesting a transient, idiosyncratic phenylalaninemia, which appears to be not uncommon among young infants. These cases, however, can be eliminated by periodic monitoring of blood phenylalanine levels, which on a low-phenylalanine diet could be expected to drop below normal (roughly 2 mg%) as the transient disturbance subsides. And monitoring is of great importance in any event, to check on the effects of the dietary regimen. Here, as elsewhere, we are learning that overtreatment, resulting in hypophenylalaninemia, may be quite as damaging as undertreatment. Moreover, clinical experience has demonstrated that individual requirements for phenylalanine among PKU patients vary greatly; one child may require three times as much dietary phenylalanine as another to maintain the same blood level. The difference, apparently, is in the rate at which the amino acid is metabolized and excreted by alternative metabolic routes.

Monitoring is no more difficult than the initial screening. Indeed, it does not even require the infant's being brought to a clinic or physician's office, since the mother can quickly be taught how to take a blood specimen in a standard filter-paper blank that can be mailed to the testing center.

Given prompt, individualized, and carefully monitored treatment along these lines, there is every reason to hope for a favorable outcome, in the sense of producing a normal, healthy child and adult. There has been much debate among pediatricians and medical geneticists over what constitutes a rational prognosis in PKU, based on the undoubted fact that treatment has seemed much more effective in some children than in others. My own belief is that much or all of this variability can now be accounted for, first by variation in the time when treatment was instituted, and, second, by the variations just cited in the "minimum daily requirement" of phenylalanine.

Whether early treatment, adjusted to the individual's metabolic needs, will prove successful in *all* cases remains to be proved; these sophisticated modalities have been employed for only a few years, so that long-term studies of such patients do not yet exist. It can be said, however, that several such studies have now passed the five-year mark, and that in all cases the IQ of the children falls into a normal distribution. Moreover, the incidence of behavioral disturbances such as hyperactivity, which are a conspicuous feature in some (though not all) cases of untreated PKU, seems no greater than normal.

The prospect that most or all PKU patients will grow up into essentially normal individuals, however, raises another health problem that will require attention: prenatal or "maternal" phenylalaninemia. Physicians have already accumulated a limited amount of experience with this condition, owing to the fact that a small but significant fraction of *untreated* PKU patients are of normal or low-normal intelligence – i.e., not so retarded as to require institutionalization and therefore (if female) not unlikely to become pregnant.

The majority of infants born to such mothers show severe retardation even though their (postnatal) serum phenylalanine levels are normal. Not infrequently we find evidence of more serious growth disturbance, such as microcephaly, which is seldom found in "ordinary" PKU. The obvious presumption is that they have been damaged by high phenylalanine levels in the mother's blood. The amino acid crosses the placenta, and studies of a pregnant monkey in which phenylalaninemia was induced by means of a special diet have shown that levels of the compound were even higher in the fetus. The equally obvious conclusion is that during pregnancy the mother should be put on a low-phenylalanine diet, and this has been done in several cases (see illustration on page 99).

Evaluation is complicated by the fact that a minor fraction of infants born to PKU mothers show no intellectual impairment. One source of this apparent anomaly may well be the previously cited "marginal" cases in which the mother's serum phenylalanine approaches normal levels: certainly in one case where all the

Newborn Screening Tests[1] for Inherited Abnormalities

Disease	*Test Substance*	*Test*	*Automated*	*Treatable*
Phenylketonuria	Phenylalanine	BIA[2]	✓	✓
Maple Syrup Urine Disease	Leucine	BIA	✓	✓
Tyrosinemia (transient and permanent)	Tyrosine	BIA	✓	✓
Homocystinuria	Methionine	BIA	✓	✓
Histidinemia	Histidine	BIA	✓	✓
Valinemia	Valine	MBIA[3]	✓	✓
Galactosemia Transferase or Kinase Deficiency	Galactose	MBIA or Coliphage	✓	✓
Transferase Deficiency only	Galactose Uridyltransferase	Beutler	Partly	✓
Argininosuccinic Aciduria	Argininosuccinic Acid Lyase	EA[4]	✓	✓
Orotic Aciduria	Orotidine-1'-phosphate Decarboxylase	EA	✓	✓
Hereditary Angioneurotic Edema	C1 Esterase Inhibitor	FST[5]	Partly	No
Emphysema (adult) Liver Disease (infant)	α-Trypsin Inhibitor	FST	Partly	No
Sickle Cell Anemia	Hemoglobin	Electrophoresis	Partly	Palliative only

1 *Using dried blood spot filter paper specimens* 2 *Bacterial Inhibition Assay*
3 *Metabolite Bacterial Inhibition Assay* 4 *Enzyme-Auxotroph Bacterial Assay*
5 *Fluorescent Spot Test*

children were of above-normal intelligence, the mother's serum phenylalanine was found to be only 10 mg%. It is also not unlikely that variations in fetal enzymes are involved here. We now know, contrary to earlier beliefs, that the enzyme phenylalanine hydroxylase is manufactured prenatally in the fetal liver, but there is doubtless appreciable variation in the time when that enzyme becomes manifest. Accordingly, there must be variation in the degree to which it can protect the fetus by metabolizing the exogenous (maternal) phenylalanine.

Be all that as it may, it is clear that with some hundreds of PKU cases being detected and treated annually, the population at risk of prenatal phenylalaninemia can be expected to rise rapidly as the "first generation" of screened and treated girls reaches childbearing age. The low-phenylalanine diet will probably be discontinued at puberty or (usually) earlier, both for practical reasons and because it may be found that phenylalanine has only minor effects, in most cases, after brain development is completed.

In principle, prophylactic dietary treatment of pregnant PKU patients should not be particularly difficult or expensive – *provided the patients are known*. This points up the importance of long-term follow-up of these individuals – many of whom may be totally unaware that they suffer from what would have been, if untreated, an incapacitating metabolic defect. What we have here is a problem in the logistics of medical information: how does the physician, knowing that his patient is at risk of producing an abnormal child 10 or 20 years from now (by which time she may well have moved a thousand miles away), ensure that she and/or her then physician have the information needed to avert the risk? The answer is certainly not a simple one – but it is relevant not merely to PKU but also to other genetic diseases, to the extent that they too are correctible and liable to affect the patient's offspring.

Considering only the United States, well over 3,000,000 neonates are now being screened for PKU annually; this, at a generous estimate, represents an outlay of something like $10 million a year. Compared to the tens of billions consumed annually by the Defense Department, or even the billions expended on space programs and superhighways, this is pretty small potatoes, but it is still big enough to draw the eyes of state legislators and budgeters seeking "frills" whose elimination can reduce the admittedly severe current demands on their funds. The first attempt to discontinue PKU screening occurred in Illinois two years ago, and though it was beaten back by the efforts of parents and physicians, similar attempts can be expected as the budgetary pinch on state governments grows tighter – which it seems likely to do over the next few years at least.

It is therefore necessary to say flatly that – and I choose my words carefully – discontinuance of PKU screening would represent not merely medical but also fiscal irresponsibility of the grossest sort. The detection and treatment of one case of PKU represents an outlay (assuming it is the outcome of 10,000 screening tests, each costing 50¢ to $4.00 in the U.S.) of up to $50,000; but failure to detect that case means a child that must almost certainly be institutionalized for the rest of its life, representing an outlay of at least $250,000 (this assumes an average life span of 50 years and an annual expenditure for custodial care conservatively estimatable at $5,000). The $250,000 figure includes no allowance for the future earnings of the treated case, or of the tax income from such earnings. It does not allow for the suffering experienced by the parents of a permanently retarded child – which is not, in any case, quantifiable in terms that are likely to make sense to a budgeter. We are not talking here about human values but purely economic ones: whether it is better to spend $50,000 now or five times that sum later.

There is, for that matter, good reason to expect that the $50,000 figure can itself be somewhat reduced. One approach to this is through the use of automated test equipment, of which I shall have more to say in a moment. However, to get full value from this

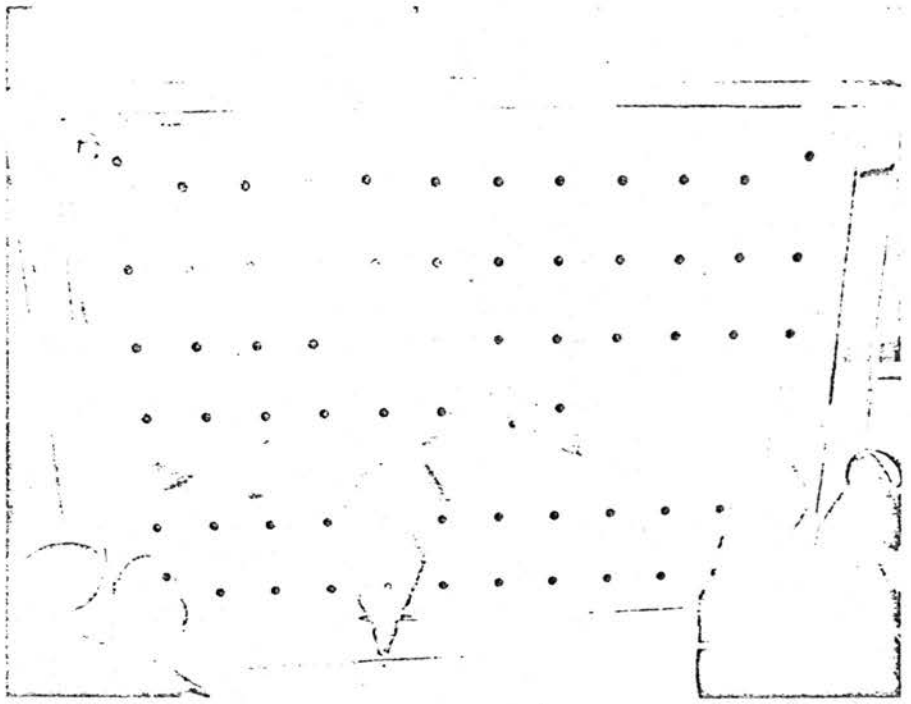
apparatus, testing must be done on a large scale: a minimum of 25,000 births a year. This constitutes a powerful argument for regionalization of screening programs; given the validity of tests based on dried blood spots, which can be mailed in to the testing center, there is no good reason why any hospital should find it necessary to carry on its own, small-scale, screening program. The centralized, consolidated programs also possess advantages from the standpoint of staff morale. A program covering only a few thousand births per year can easily run for several years without turning up a single true case of PKU, so that the personnel involved may acquire the feeling they are engaged in a pointless exercise. When the screening load reaches the level of 50,000 or 100,000 per year, however, the expectable number of cases will provide tangible evidence that the program is performing a valuable prophylactic function.

It would be misleading, however, to suggest that the cost of screening is likely to be markedly lowered by even the most rational organization of these programs. The main cost factor is, and will remain, the actual gathering of specimens and the necessary follow-up on positive tests; the actual processing is a relatively minor item. Authorities in New Zealand, for example, find that with automated equipment the entire testing load – some 50,000 New Zealand births per year, plus several thousand others mailed in from various Pacific islands – can be easily handled by one person, whose work includes preparing and "seeding" the culture trays, placing the test discs on them, and reading the results. The economics of mass screening will continue to rest, as they do now, on the demonstrated fact that prevention is cheaper than nonprevention.

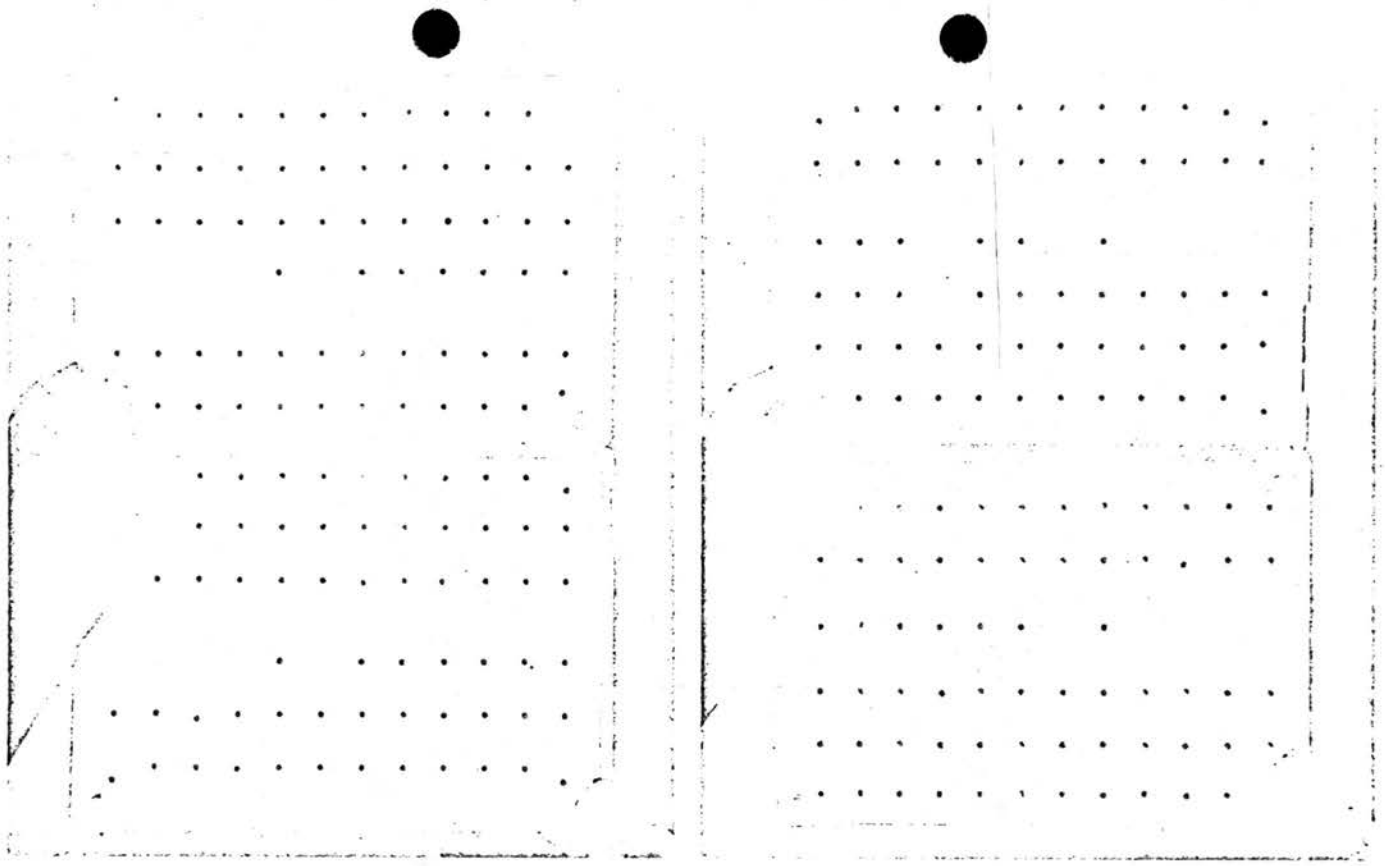
The automated equipment grew out of the finding that the inhibition assay procedure can be adapted to the detection of several other hereditary aminoacidemias simply by varying the inhibitor dissolved in the culture medium. These conditions include valinemia, tyrosinemia, histidinemia, homocystinuria (in which we test for methioninemia), and maple syrup urine disease (leucinemia). With automation, all these tests plus the phenylalanine test can be carried out at no more cost than the latter alone, unautomated.

The machine, called a punch-indexer, handles test specimens in batches of 56. It automatically punches out four ⅛-inch discs from each specimen blood spot and transfers them to predetermined locations on four different culture trays, each containing a different inhibitor – in each case, of course, the same spatial location for a given specimen. The testing array is completed with four control discs, one in each corner, as a check on uniformity of the medium, and a row of up to 12 control discs across the center of the tray, which contain blood (taken from the "expired" bottles of a blood bank) loaded with several standard concentrations of the amino acid in question. In PKU testing, for example, we use discs with normal, 2, 4, 6, 8, 10, 12, and 20 mg%; since each of these produces a growth zone in the culture of differing width, any positives in the test specimens can be approximately quantified immediately by visual comparison with the range of control discs.

Much the same mechanized procedure can be used for large-scale testing to unearth other metabolic defects, though the biologic and chemical rationales differ somewhat. Galactosemia, for instance, can be detected by the metabolite inhibition assay test, here employing a mutant strain of *E. coli*. (The principle for this test was suggested by Dr. Kenneth Paigen, Roswell Park Memorial Institute, Buffalo, N.Y.) This organism has the same metabolic defect as human galactosemics, so that galactose (or galactose-6-phosphate, in another form of the disease) accumulates in the cells, inhibiting growth. The diameter of the "zone of inhibition" (as opposed to the "zone of growth" in the tests described earlier) is proportional to the amount of galactose in the specimen disc. The same test can detect valinemia, since *E. coli* growth is inhibited by valine also. Galactosemia of one type can also be diagnosed by the Beutler test, which is chemical rather than biologic and measures enzyme activity directly rather than the accumulation of an unmetabolized substrate. The Beutler test involves a reaction between the enzyme galactose uridyltransferase, present in normal erythrocytes, and a synthetic substrate, the product of which is fluorescent. For the test,



Chief technician Emerson Barr examines agar tray that, after incubation overnight, shows one positive PKU result requiring follow-up of the infant. This can be seen in row 3 from top; "halo" surrounding disc indicates that phenylalanine in blood sample prevented the usual inhibition of growth of B. subtilis *by the β-2-thienylalanine present in medium. Row 4 contains control discs with known concentrations of phenylalanine.*



Shown above are results of additional bacterial inhibition assays. Trays at left were tested with phenylalanine (top) and tyrosine (below; positive can be seen in row 5, below control discs; each tray corner also has control disc). Trays at right show (top) tests of leucine (for maple syrup urine disease), with no positives, and (below) methionine (homocystinuria, one positive in row 4).

blood-specimen discs are placed, by the same machine, in "dimples" in a plastic tray, each of which serves in effect as a miniature test tube for the reaction. A solution of the substrate is added and, after incubation, a failure to fluoresce points to enzyme-deficient cells.

Direct assays of enzyme activity are generally considered superior to assays of the enzyme substrate, since they measure the metabolic defect itself rather than its consequences. Unfortunately, however, enzyme assays cannot be performed in PKU, since the enzyme in question is found only in the liver. Several other inborn errors, however, resemble galactosemia in that the "missing" enzyme is a normal constituent of erythrocytes, and is not destroyed by drying, so that its presence or absence can be detected in blood-spot samples.

Two of these tests, developed by Dr. William Murphey in our laboratories, are of the Enzyme-Auxotroph Assay type, employing mutant strains of *B. subtilis*. One strain, for example, requires exogenous arginine for growth; it cannot produce the amino acid from a medium containing the substrate argininosuccinic acid. Normal erythrocytes, however, contain the enzyme argininosuccinic-acid lyase, which liberates arginine from that substrate, permitting the organisms to grow. If the organisms fail to grow, the enzyme is absent from the specimen, which is to say that the individual suffers from argininosuccinic aciduria. A similar test with a different bacterial strain can detect absence of orotidine-1′-phosphate decarboxylase, which is the underlying defect in orotic aciduria. Altogether, some 20 different enzyme activities can be detected in dried blood from normal neonates by one or another means. For most of these there are as yet no known instances of congenital absence or inactivity of the enzymes involved, so there has been no attempt to adapt the tests to mass screening.

In addition to clinical conditions produced by enzyme deficiencies, there are also conditions resulting from a deficiency in an enzyme inhibitor. Recently, Dr. Murphey has developed two simple and accurate fluorescent spot tests, applicable to the dried spots of blood, for inherited deficiencies of enzyme inhibitors. One of these, inherited as a Mendelian autosomal dominant trait, is hereditary angioneurotic edema, associated with a deficiency in C1 esterase inhibitor. Although several hundred cases have been listed in the literature, mass newborn screening reveals it to be a very rare condition. The second condition, α-antitrypsin deficiency, inherited as a Mendelian recessive trait, appears to be more frequent, since it has been claimed to be associated with at least 1% or 2% of all cases of emphysema. It can also be associated with infantile liver disease. Its true frequency remains to be determined, since routine screening of newborns for this condition has only just begun.

It is likely that other enzyme deficiencies exist but are sufficiently uncommon to have thus far escaped detection. Alternatively, such defects could be not uncommon but associated with little or no impairment of physiologic function. This appears to be the case, for example, in many or most types of glycinuria, several cases of

which have been discovered accidentally in the course of other, unrelated investigations. Because clinical and research attention has, for obvious reasons, been focused on pathologic errors of metabolism, we have doubtless overlooked many anomalies whose functional effects are obscure or benign. Yet I believe that with increasing knowledge it will become clear, as Garrod suspected more than 60 years ago, that pathologic inborn errors are in fact only exaggerations of the innate chemical differences present in all of us.

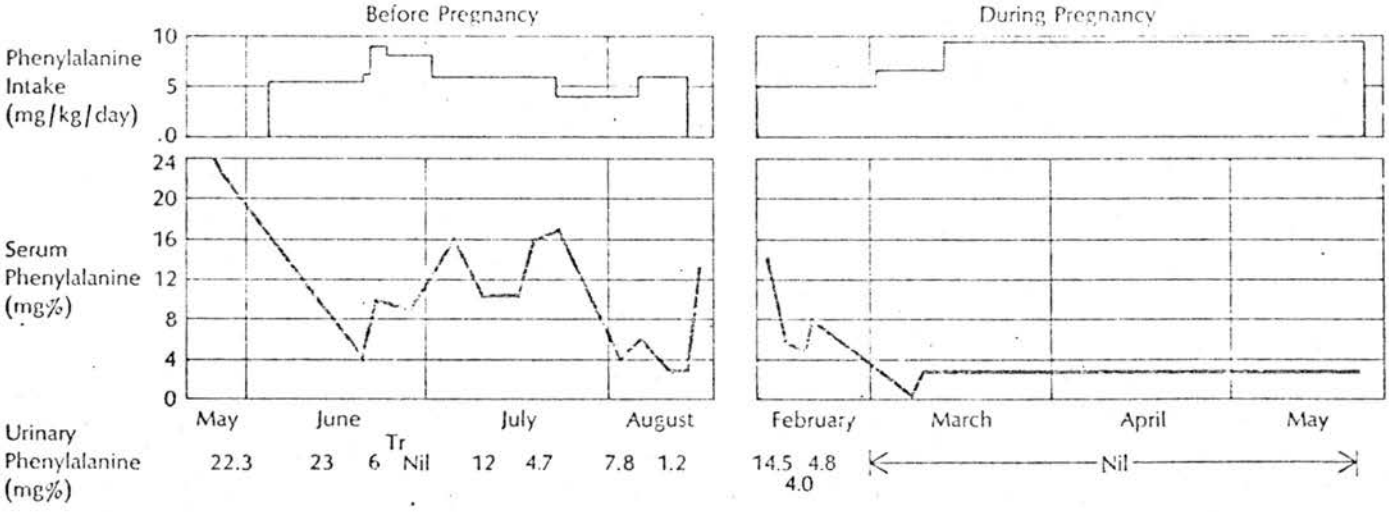
Recently, a practical method of using the newborn dried blood spot (or specimen) in mass screening for sickle cell hemoglobin and other hemoglobin variants has been developed by Dr. Michael Garrick in our laboratory. This method uses discs punched and placed by the punch-index machine in the dimples in the plastic dimple-tray. These discs are then eluted in the dimples, after which the eluates are used for electrophoretic separation of hemoglobin bands in cellulose acetate strips. A follow-up procedure, using agar electrophoresis, can differentiate the SA heterozygote from the SS homozygote. Using this procedure, filter paper specimens for the PKU test can be screened by a laboratory already performing multiple tests on the specimens at a material cost of $0.03 per specimen. The capital investment for equipment is less than $1,000 to acquire the capability for screening up to 100,000 specimens per year.

This screening procedure is the first one to be developed by our laboratory that permits detection of the "carrier" heterozygote by mass screening. It is also the first procedure developed anywhere, to our knowledge, that permits detection of S hemoglobin in the newborn infant by mass screening, in spite of the presence in such specimens of more than 90% fetal hemoglobin. Because of the recent increased interest in prevention and treatment of sickle cell disease within the United States, it is hoped that this test will receive a large-scale trial in the near future.

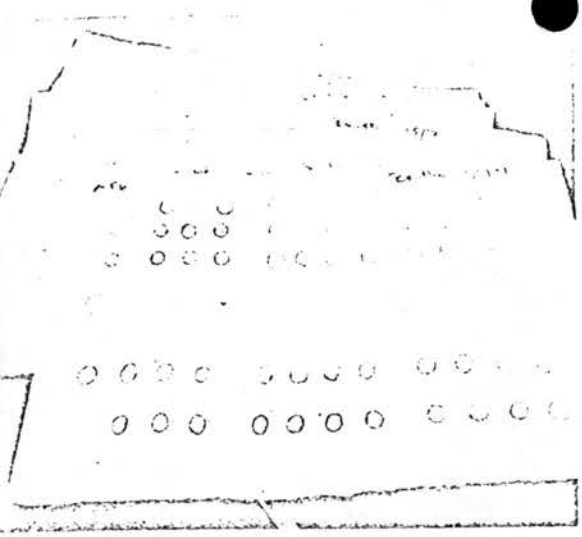
During the past five years the screening laboratories collaborating with me have demonstrated that, with automation, six to eight of the tests described above can be carried out at little increase in cost over the single PKU test, providing a sufficient volume of specimens are available. The minimum is approximately 25,000 per year; increasing volume further reduces the cost and produces other advantages. For these reasons, we have recently been proposing development of model, or demonstration, "regional" centers for inborn errors of metabolism.

By "regional" program, I mean, first of all, one in which a sufficient number of newborn specimens are screened daily to permit application of those methods of automation already routine in a number of laboratories for the purpose of carrying out at least 8 of the 13 tests available.

Even more important for such a program is close and continuous liaison between the screening center and the medical follow-up and management of the cases detected in screening. Several programs with these features have been developed in the past few years in Europe and in New Zealand. In fact, although approximately 24 multiple-test laboratories, using four or more of my tests on the dried spots of blood collected for PKU screening, have come into existence since 1964, almost all of these are located in other countries except for the original four in the U.S., which have been working with me as part of a joint collaborative effort. However, the health departments of Ohio and Maryland recently purchased punch-index machines and have now begun multiple testing. This occurred as a result of a conference we held in February 1971.



That control of phenylalanine levels in the pregnant PKU woman can ward off mental retardation in her offspring is indicated in records above of patient reported from Dublin by Allan and Brown. This patient had borne three children observed in school to be mentally retarded; her urine was strongly positive for phenylketones, that of the children negative. Detailed investigation found no explanation other than high intrauterine phenylalanine for the mental deficiency in the children. In the first phase of the study graphed above, efforts were made to determine whether a low-phenylalanine diet could effectively reduce the mother's serum levels; this was accomplished during three months of hospitalization (spikes in graph at left reflect breaches in the diet when a night attendant "took pity" on the patient and gave her a glass of milk). When she subsequently became pregnant, she reentered the hospital for dietary maintenance during the last five months. At birth the fourth child had a cord blood level of 7.6 mg% phenylalanine; at 6 hours the serum level was 5.2 and at 48 hours a normal 1.4. Tests later showed normal intelligence.



Beutler test for one type of transferase deficiency assays enzyme activity on a synthetic fluorescing substrate added to discs; spots that do not fluoresce under UV light after incubation are positive.

The three principal problems in our own country that have impeded expansion of PKU test programs to include tests for other conditions are:

1) Lack of liaison between screening centers and medical centers;

2) Restrictions of screening areas by state boundaries, as states often contain too small a population of newborn infants per year for efficient PKU screening, let alone screening for more rare conditions;

3) Fragmentation of screening, even within large states, when private facilities are used. An outstanding example is California, where, I am told by a health department official, newborn tests for PKU are carried out by more than 200 different private laboratories at a charge that varies from $1 to $15 per test! With the same funds, one or two regional centers could test all infants for a dozen conditions and have more than half of the money left over to assist with medical follow-up and management.

If a continued search for these and other rare or obscure biochemical anomalies has (as yet) no "practical" value, in the sense that they involve either diseases for which no treatment exists or a disease that need not be treated, it nonetheless seems to me to possess great scientific importance. I would say it has enough scientific value to encourage mass screening for as many biochemical anomalies as possible, always assuming that this can be done without dipping into funds needed for more urgent aspects of health care.

An obvious approach to this is to expand the "six-for-the-price-of-one" achievement that automation has already brought to screening into a "20-or-30-for-the-price-of-one" arrangement. Already our laboratory is working on several approaches to this goal; all of them involve not simultaneously testing several specimens from the same individual for different anomalies, as is done with the punch-index machine, but testing a single specimen simultaneously for several anomalies.

One possibility is a "multiple inhibition assay," involving the addition of two (or more) antimetabolic analogues to the culture medium in such concentrations that the culture would respond to *either* of the abnormal constituents if present in any specimen. Thus, if one added 4-azaleucine plus β-2-thienylalanine at appropriately low concentrations, the culture should, in theory, respond to either leucine or phenylalanine. Thus far, however, we have been unable to devise such tests in a form suitable for routine use.

Another, and currently more promising, approach involves two or more strains of *B. subtilis*, each one resistant to all but one of the inhibitors used. Again a response is produced to any of several abnormal serum constituents. Yet another approach, which we call the "multiple auxotroph" test, again employs mutant strains, but this time each of the mutants requires a different amino acid for growth. A mixture of strains requiring, respectively, phenylalanine, leucine, and histidine, for instance, would respond to PKU, maple syrup urine disease, and histidinemia. A cardinal difficulty here is that the mutants can interact when mixed, for reasons still obscure, producing either inhibition or stimulation of growth. However, two such multiple tests appear promising.

In all these instances, of course, a positive response could mean *any* of the several conditions the test was designed to respond to, with differential diagnosis requiring further tests. These, however, would involve only a few score or at the most a few hundred specimens, as against the tens of thousands eliminated by the initial multiple screen.

Given the further development and perfection of multiple screening tests, mass screening can become not merely a way of rapidly detecting PKU and other treatable genetic diseases but also a source of invaluable information on biochemical differences in large populations. Given the fact that screening for PKU alone has proved itself not merely medically but also economically sound – which seems to me unarguable – we can (one hopes!) safely assume that specimens will continue to be collected by the hundred thousand and screened by one or another technique. And if that is the situation, it is surely only common sense to seek screening procedures that, for the same outlay, will yield steadily increasing "fringe benefits" of data on both pathologic and benign innate metabolic differences. □

Selected Reading

Allan JD, Brown JK: Maternal phenylketonuria and foetal brain damage. An attempt at prevention by dietary control. Some Recent Advances in Inborn Errors of Metabolism. Holt KS, Coffey VP, Eds. E. & S. Livingstone Ltd., Edinburgh and London, p 14, 1968

Guthrie R: Screening for "inborn errors of metabolism" in the newborn infant – a multiple test program. Birth Defects Original Article Series IV. p 92, 1968

Guthrie R: Screening for phenylketonuria. Triangle 9:104, 1969

Murphey WH, Patchen L, Guthrie R: Screening tests for argininosuccinic aciduria, orotic aciduria, and other inherited enzyme deficiencies using dried blood specimens. Biochem Genet 6:51, 1972

Proceedings of the International Symposium on Phenylketonuria and Allied Disorders, Tel Aviv, June 15-22, 1969. Cohen BE, Rubin MI, Szeinberg A, Eds. Translators' Pool, Israel, 1971

MacCready RA, Levy HL: The problem of maternal phenylketonuria. Am J Obstet Gynecol 113:121, 1972

FROM: H. L. LEVY & J. P. KENNEDY. GENETIC SCREENING FOR INBORN ERRORS OF METABOLISM. U. S. DEPT. OF HEW P[illegible] No. [illegible]

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Efron, an active clinical and basic researcher in the inborn errors of metabolism at the Massachusetts General Hospital. This type of relationship has been continued and even strengthened by those who are now in charge of the Massachusetts program and who are active at both the state laboratories and the medical center. Consequently in Massachusetts the physicians who conduct the screening program also evaluate and care for many of the patients. Thus both aspects of genetic screening can be evaluated in an integrated manner. It may be that associations such as this will lead to a reciprocal relationship between public health facilities and medical centers in many other areas of health care.

Organization of Screening

In addition to leading to lower unit costs, large screening programs are also in a better position to evaluate the technical and medical aspects of screening than small programs. Centralized facilities in Austria, Massachusetts, and Australia each perform hundreds of thousands of tests yearly. The experience gained by doing so many tests results in technical expertise. Furthermore, with the relatively large numbers of affected infants discovered in such programs, wide experience is gained in the biochemical spectrum of each disorder. Conversely, programs in which only a few hundred or even a few thousand infants per year are tested lack this necessary experience.

Ideally, genetic screening should be organized within public facilities on at least a regional basis. Thus in the United States a single laboratory could test 500,000 to a million infants a year from several states in a region. A similar organization of screening could be established in Europe across national boundaries. Evaluation and treatment centers could be established at local and state levels in cooperation with medical centers.

Cost versus Benefit

The costs of genetic screening, both tangible and intangible, are considerable, as has been noted above, and must be weighed against the resulting benefits to individuals and to society. These benefits may include those that are economic as well as those that are humanistic. In terms of economics, only PKU screening would seem to clearly meet the standards of efficiency at the present time. For instance, each year in a population of 100,000 newborns, seven could be expected to have PKU. If none received treatment and if three to four each subsequently

Screening for Congenital Metabolic Disorders in the Newborn Infant: Congenital Deficiency of Thyroid Hormone and Hyperphenylalaninemia

Committee on Genetics

Charles R. Scriver, M.D., Chairman; Murray Feingold, M.D.; Peter Mamunes, M.D.; *and* Henry L. Nadler, M.D.

Consultants: Barton Childs, M.D.; Jean H. Dussault, M.D.; Neil A. Holtzman, M.D.; Parvin Justice, Ph.D.; *and* Rueben Matalon, M.D.

The Committee on Genetics of the American Academy of Pediatrics was formed in 1976. The initial reports from the Committee are published in this supplement to *Pediatrics:* one on guidelines for screening the newborn infant for hyperphenylalaninemia (including phenylketonuria [PKU]) and the other on screening for congenital hypothyroidism.

The first statement describes guidelines for screening for thyroid hormone deficiency in newborn infants: it concerns a traditional problem in pediatrics, the prevention of cretinism. A statement on "T_4 screening" has already been issued by the American Thyroid Association.[1] Why is there need for another (and longer) statement from the Academy? The Task Force on Genetic Screening recommended a special review of T_4 screening, and that recommendation has been acted on quickly in the hope that most of the mistakes made in PKU screening will not be repeated in T_4 screening. The American Thyroid Association statement adequately describes the status of testing for T_4 deficiency; it does not cover other essential components of an effective screening program, namely, provision for serving patient retrieval, diagnosis, and treatment. The Committee urges pediatricians and endocrinologists who elect to push ahead with T_4 testing to pause and examine the many issues of mass newborn infant screening before they act too hastily, perhaps to the detriment of their patients and newborn infant screening programs.

Dr. Jean Dussault served as consultant to the Committee when it examined T_4 screening; his personal experience extends to ¼ million screened subjects and emanates from a model program which has largely avoided many pitfalls of newborn infant screening. After reviewing that experience and examining it with the existing problems of PKU screening in mind,[2] the Committee could not recommend universal (mass) T_4 screening for a region in the absence of an advisory committee and an integrated screening program with supporting services.

The statement on screening for hyperphenylalaninemia was prepared by Dr. Neil A. Holtzman; it is intended to help pediatricians and their associates avoid the pitfalls surrounding newborn screening, which are delineated in the report from the National Academy of Sciences on Genetic Screening.[2] Screening for hyperphenylalaninemia is still evolving as an effective public health activity. For example, a newly recognized form of PKU caused by dihydropteridine reductase deficiency was discovered long after screening programs for neonatal hyperphenylalaninemia were well instituted. It is now essential to distinguish this variant from other causes of hyperphenylalaninemia for purposes of prognosis, treatment, and counseling; this imposes new requirements for backup services on the screening programs. The need for a regional commission or an advisory committee[2,3] to guide the development of new resources and to evaluate the performance of existing services is one of the lessons learned from past experience with PKU screening.[3]

This screening supplement does not consider screening for other congenital metabolic disorders which may be of interest to pediatricians, e.g., galactosemia, cystic fibrosis, and maple syrup urine disease. The principal reason for not making additional statements now is our belief that the regional advisory committees or commissions can make these decisions about implementation of "add-on" screening tests. The capabilities for the region will depend on the organization of the existing screening program. If a regional commission does not exist, the committee urges those responsible for the screening programs to familiarize themselves with the concept[2,3] and to act accordingly.

REFERENCES

1. Newborn Committee of the American Thyroid Association: Recommendations for screening programs for congenital hypothyroidism. J Pediatr 89:692, 1976.
2. National Academy of Sciences: Genetic Screening: Programs, Principles and Research. Washington, DC, National Academy of Sciences, 1975.
3. Task Force on Genetic Screening: The pediatrician and genetic screening (every pediatrician a geneticist). *Pediatrics* 58:757, 1976.

ACKNOWLEDGMENT

The Committee acknowledges the advice and assistance of Dr. Reuben Matalon, Dr. Parvin Justice, and Dr. Jean Lockhart, Director, Department of Committees of the American Academy of Pediatrics.

Screening for Congenital Deficiency of Thyroid Hormone

The Task Force on Genetic Screening was not able to discuss details of the various forms of genetic and metabolic screening.[1] A Committee on Genetics was formed to examine these and other issues relating to congenital disease and medical genetics. The following statement is one of the Committee's reports.

Congenital thyroid hormone deficiency is a prime example of a condition whose early diagnosis, as well as the opportunity for effective treatment, can be missed. The following report examines both the practice of newborn infant screening for early diagnosis of congenital thyroid hormone (T_4) deficiency and the relation of that activity to the principles of metabolic (and genetic) screening.[2] The reader is also referred to a parallel statement prepared by a committee of the American Thyroid Association.[3]

BACKGROUND INFORMATION

There is limited placental transport of thyrotropin (TSH) and the thyroid hormones 3,5,3'-triiodothyronine (T_3) and thyroxine (T_4). Serum T_4 concentration in the newborn infant will be diminished when there is congenital deficiency of thyroid tissue, impaired activity of one of the enzymes involved in thyroid hormone biosynthesis (T_4 hormone dysgenesis), deficient serum T_4 binding globulin (TBG), or deficient stimulation of thyroid (by TSH) or pituitary (by thyrotropin releasing hormone [TRH]). Primary congenital hypothyroidism (cretinism) is associated with a high frequency of mental retardation; cretinism accounts for about 1% to 2% of admissions to institutions for the mentally retarded. Only half of the patients with cretinism achieve IQs above 90 if diagnosis and treatment are delayed until 3 to 6 months of age, but 75% of patients achieve this outcome when clinical diagnosis is made and treatment begins before 3 months of age.[4] It has yet to be determined whether diagnosis and treatment within the first month of life can further improve the outcome.

An accurate radioimmunoassay system is available to measure T_4 concentration in body fluids; a corresponding assay is also available to measure TSH in body fluids. Accordingly, newborn infant screening for congenital hypothyroidism is now possible. The combined application of the T_4 and TSH assay facilitates newborn infant screening and enhances specificity and sensitivity of the process. (Specificity and sensitivity have precise meanings in screening terminology. *Specificity* is the ability of the screening test to exclude normal subjects from false detections. *Sensitivity* is the ability of the screening test to detect subjects with the abnormality.) The objective of T_4 screening in newborn infants is to obtain early diagnosis and initiate treatment at the incipient stage of hypothyroidism.

Many infants (in fact, 425,000) have already been screened for T_4 deficiency in five pilot programs. (The five programs were carried out in Quebec, 250,000 infants; New England, 70,000; Oregon, 64,000; Pittsburgh, 25,000; and Toronto, 16,000. These data are valid up to September 1976.[5]) Among these, 72 infants (or 1 in 5,900 live births) were confirmed to have primary or secondary congenital hypothyroidism and 6 others have inherited defects in the biosynthesis of T_4 (dyshormonogenesis). However, at least 36 additional infants (31.6%) have TBG deficiency as the cause for their positive T_4 screening test results. The total number of infants with a diagnosed cause for decreased serum T_4 concentration is 114 in the 425,000 tested in these pilot programs, of which 68.4% required specific treatment. Only two patients with congenital hypothyroidism have apparently been missed in these screening programs: one infant escaped diagnosis because he was not actually screened (apparent sensitivity = 78/80 for the screening programs); the other was missed by the test (apparent sensitivity = 78/79 for the test). This is an excellent, effective, early "track record" for a new form of mass screening of newborn infants; the record indicates a requirement for an effective screening program and a reliable test.

T_4 SCREENING: DETAILS

The technical aspects of T_4 testing and screening are critical for its success. Attention to details, both for the test and the program, accounts for the acceptable sensitivity of the initial pilot programs.

Tests

The T_4 radioimmunoassay can be applied either to dried blood spots on filter paper (Schleicher and Schull, No. 903)—collected from a heel prick or from cord blood—or to serum. One of the two recommended assays[6,7] should be used.

The TSH radioimmunoassay[8,9] can also be done on the filter paper blood specimen or on serum. Specificity of screening is augmented and economic costs are reduced when the TSH assay is applied to the same sample evincing a low T_4 level.

Measurement of reverse T_3 in blood or serum is unlikely to be a useful adjunct for newborn infant screening.[5]

The use of heel prick blood obtained at discharge from the nursery is recommended in preference to cord blood samples; specificity of the T_4 and TSH tests is better on heel prick blood.[3,5]

Specificity

False-positive test results (i.e., low T_4 levels without deficient gland activity or TBG deficiency) will occur. The lowest possible frequency of such results (highest specificity) is an essential objective of an effective T_4 screening program. Experience indicates[10] that 1.84% of filter-paper samples yield a "low" T_4 concentration (positive test). A low value by the assay applied to filter-paper, heel-blood samples is defined as a value less than 2.3 SD from the geometric mean for the day,[10] uncorrected for the weight of the infant.[11] Such precision in the cutoff level for delineation of a "low" T_4 concentration can be obtained only in a laboratory processing many samples daily under rigorously standardized conditions. The majority (98.4%) of these "positive" test results are false-positive.[10]

Attention to the birth weight of the infant permits a corrective factor to be applied, which reduces the frequency of false-positive T_4 test results by 0.15%.[11] The age of the infant does not influence the T_4 test result. A further reduction in the frequency of false-positive test results follows the application of TSH assay to the 1.84% of samples with a low T_4 value. A TSH concentration greater than 1.0 μU on filter-paper spots of heel blood indicates a "positive" test. When T_4 values (< 2.3 SD from the geometric mean) and TSH levels (1.0 μU) are combined, the number of recalled subjects falls to 1.1%.[10] Further improvement of specificity is, at present, considered unlikely without sacrifice of sensitivity in the screening program. A protocol to maintain maximum specificity and sensitivity has been developed at one center with extensive experience[10] (see Appendix).

Sensitivity

False-negative test results will occur in any screening program. The lowest possible frequency of such results (highest sensitivity) at a reasonable cost should be the most desired objective of the program.

The frequency of false-negative tests results ("normal" blood T_4 value with deficient thyroid gland activity) will be determined by the level of the cutoff value which defines a "low" T_4 concentration. This value will vary from day to day in large testing programs, and this variance should be taken into consideration in designing T_4 screening programs.

Screening for congenital hypothyroidism either by the T_4 or TSH assay alone is not advised.[5] Both tests must be available for an effective program.

Cost of Testing and Screening

The cost of the T_4 test on a filter paper blood sample or a cord blood sample is about 60 cents per test, and the TSH test is currently about $1.50 per test (1976 U.S. dollar value).[3] These relative costs may vary in other countries. The cost for screening (versus testing) will be higher because of the need for a program to maintain the process of screening, which includes several components (sample collection, laboratory analysis, record keeping, follow-up of patients, repeated testing, diagnosis, counseling, and treatment). De novo screening for T_4 deficiency will be an expensive undertaking for any community; however, for communities with existing screening structures, the added cost of T_4 screening is marginal.

STRUCTURE AND PROCESS OF T_4 SCREENING

The process of T_4 screening demands a high standard of technical competence. Validation of new programs will be extremely important if the pitfalls experienced with PKU screening are not to be repeated with the expansion of T_4 screening. The occasional use of the commercial T_4 tests now being offered—at ten times the present cost for mass T_4 screening tests—does not offer the

pediatrician or his local laboratory the essential, statistical resource required for interpretation of the T_4 test in newborn infants or the mandatory backup testing with a TSH assay.

Genetic (or metabolic) screening in the newborn infant is a process that requires an integrated structure.[1,2,12] The rationale for T_4 screening is to permit early medical intervention through the process of early diagnosis of congenital hypothyroidism. To fulfill this objective, the T_4 screening program must encompass four basic subobjectives: (1) testing, (2) patient retrieval, (3) diagnosis, and (4) follow-up (and counseling and treatment). The process by which each of these objectives is attained requires an appropriate structure.

Testing

The pediatrician must be reassured that specificity and sensitivity of T_4 testing are satisfactory. Analysis of the experience with PKU screening[2] reveals that specificity and sensitivity are maximized when testing is centralized and carefully standardized in a well-designed regional program.

The time elapsed at room temperature between collection of the sample and analysis in the laboratory can influence specificity of T_4 screening[6]; long delays cause a decrease of T_4 concentration in blood spots. A low compliance rate with sample collection in the nursery is also undesirable because this can decrease sensitivity for the program.

An efficient testing structure can be achieved by a working regional advisory committee, as in the Quebec experience,[12] or through an advisory commission, as in the Maryland experience.[2]

Patient Retrieval

Rapid diagnosis and treatment are considered essential to minimize the harm of congenital hypothyroidism. A presumptive positive screening test is a signal to retrieve the patient quickly for diagnostic studies. Any delay in performance of the screening test and any further delay in patient retrieval postpones diagnosis and treatment. Analysis of the experience with PKU screening[2] revealed that too much time elapsed in many programs between birth and retrieval of the patient and initiation of follow-up investigation. Pediatricians should insist that follow-up procedures are efficient and available. In one program[12] now performing mass T_4 screening on more than 90,000 infants per year, the program was permitted by the regional medical society to contact the patient directly at the time the physician is notified. Patient retrieval is efficient and elapsed time was shortened under these conditions. This "unorthodox" approach to patients can be achieved without harmful anxiety when the community is broadly informed about the program and follow-up is done with care for the concerns of the patient.

Diagnosis

Prognosis and management are dependent on diagnosis. A positive T_4 test (low blood T_4 concentration) is not equivalent to a diagnosis of congenital hypothyroidism. Among the 114 patients with positive screening tests reported in the pilot programs,[3] follow-up investigation revealed several diagnoses, including TBG deficiency (a harmless variant constituting 31.6% of diagnoses), pituitary deficiency (6.5%), and dyshormonogenesis (8.6%). Prognosis is different for each of these conditions. Additional diagnoses may emerge in future programs, including "new" disorders not currently recognized. The pediatrician should be reassured that the regional T_4 screening program includes a competent endocrinologist. Referral of the patient with a presumptive positive test for consultation is strongly recommended, unless the physician is personally familiar with all aspects of the differential diagnosis.

Follow-up

The rationale for screening for congenital hypothyroidism in the newborn infant is to permit early medical intervention, that is, treatment with thyroxine. Prognosis and outcome will be related not only to diagnosis but also to the age at onset of treatment and the effectiveness of therapy. It is not known yet whether early treatment of congenital hypothyroidism (primary or secondary or the various forms of hormone dysgenesis) can overcome completely the effect of hormone deficiency up to the time of diagnosis. This is why mass T_4 testing should be promoted within the context of an integrated screening program with facilities and support for long-term follow-up and evaluation.

ROLE OF THE PEDIATRICIAN

The pediatrician should be an advocate of well-designed screening programs for congenital hypothyroidism, and he should recognize that T_4 testing is different from screening for congenital hypothyroidism. T_4 testing is only one component of a screening program. The pediatrician should advocate the establishment of a regional advisory committee to ensure that testing is performed

with due recognition of the problems in maintaining high specificity and sensitivity. Integration of the resources for retrieval, diagnosis, treatment, and follow-up should be attempted. The pediatrician is an ideal advocate to advise the community of the rationale for this type of screening in newborn infants. Parents deserve to know in advance that the test is being done and why.

RECOMMENDATIONS

The opportunity to establish newborn infant screening programs for the early detection of congenital T_4 deficiency is an exciting development. It is an opportunity to eliminate a serious traditional problem in pediatrics that can be distressing both to the patient who, if not detected early, may not benefit from treatment, and to the physician who, regrettably, makes a late diagnosis. One purpose of this statement is to stress that T_4 screening is more than testing newborn infants for low blood T_4 levels. Testing is no panacea unless it is done with extreme care. The effectiveness of testing will be diminished unless there is a comprehensive program to accommodate the separate processes of testing, patient retrieval, diagnosis, and follow-up.

The Committee offers the following recommendations.

1. Testing programs designed to identify a low blood T_4 concentration in newborn infants should validate the T_4 radioimmunoassay before proceeding beyond the pilot stage. Thereafter, the testing process should be rigorously controlled.

2. Heel prick blood collected on filter paper at the time of discharge from the nursery is the preferred sample. A statistical definition of the normal T_4 value is essential to define the "low" value. A large volume of samples and a central testing laboratory will enhance specificity of the test.

3. Backup testing with TSH radioimmunoassay is essential to improve specificity of T_4 screening. The TSH assay should be validated. The program should be designed so TSH testing, when indicated, is done on the same sample with the low T_4 concentration. A protocol for repeated testing and callback of patients should be defined.

4. There should be efficient delivery of samples from the nurseries to the testing laboratory and an effective system for retrieval of subjects with presumptive positive test results. The elapsed time between birth and confirmatory testing for primary congenital hypothyroidism should not exceed $3^1/_2$ weeks.

5. Diagnostic facilities should be available to investigate the patient with a presumptive positive test. A low T_4 concentration in blood may indicate primary or secondary congenital hypothyroidism, various forms of hormone dysgenesis, or serum TBG deficiency; other diagnoses may also be discovered. Prognosis and management will vary with the diagnosis.

6. Therapy by 1 month of age should be the major objective in any program screening for congenital hypothyroidism. Monitoring of treatment and evaluation of outcome should both be supported by the program.

7. A regional advisory committee is recommended to initiate a complete screening program and educate the community served by the program.

8. The pediatrician is a welcome advocate and participant at all levels of the program.

REFERENCES

1. Task Force on Genetic Screening: The pediatrician and genetic screening (every pediatrician a geneticist). *Pediatrics* 58:737, 1976.
2. National Academy of Sciences: Genetic Screening: Programs, Principles and Research. Washington, DC, National Academy of Sciences, 1975.
3. Newborn Committee of the American Thyroid Association: Recommendations for screening programs for congenital hypothyroidism. J Pediatr 89:692, 1976.
4. Klein AH, Meltzer S, Kenny FM: Improved prognosis in congenital hypothyroidism treated before age three months. J Pediatr 81:912, 1972.
5. Newborn Committee of the American Thyroid Association: Minutes of September 16, 1976, meeting. Unpublished manuscript.
6. Dussault JH, Coulombe P, Laberge C, et al: Preliminary report on a mass screening program for neonatal hypothyroidism. J Pediatr 86:670, 1975.
7. Larsen PR, Broskin K: Thyroxine (T_4) immunoassay using filter paper blood samples for screening of neonates for hypothyroidism. Pediatr Res 9:604, 1975.
8. Dussault JH, Parlow A, Letarte J, et al: TSH measurements from blood spots on filter paper: A confirmatory screening test for neonatal hypothyroidism. J Pediatr 89:550, 1976.
9. Larsen PR, Merker A, Parlow AF: Immunoassay of human TSH using dried blood samples. J Clin Endocrinol Metab 42:987, 1976.
10. Dussault JH, Morissette J, Letarte J, et al: Follow-up approach for a screening program for neonatal hypothyroidism. Unpublished manuscript.
11. Dussault JH, Morisette J, Fiset P, et al: Factors influencing results for thyroxine concentration in blood as measured in paper filter spots in a screening program for neonatal hypothyroidism. Clin Chem 22:1392, 1976.
12. Scriver CR, Clow CL, Laberge C: Genetic screening and allied services: Structure, process and objective. in Raine DN (ed): Medical-Social Management of Inherited Metabolic Disease. Liverpool, England, M and S Publisher, to be published.

STATEMENT OF COMPLIANCE WITH

MANUAL OF RULE MAKING PROCEDURES

I, Special Assistant Attorney General TERRY P. O'BRIEN, do hereby declare that I have examined the proposed rules relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation and all related documents and that, based on such examinations and my personal familiarity with the applicable procedures, the Manual of Rule Making Procedures has been followed.

Dated: 17 Feb, 1979

(Name)
Special Assistant
Attorney General

STATE OF MINNESOTA

COUNTY OF HENNEPIN

BEFORE THE MINNESOTA

COMMISSIONER OF HEALTH

In the Matter of Proposed Amendments to 7 MCAR § 1.172 Relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation

ORDER ADOPTING RULES

The above-entitled matter came on for hearing before the Minnesota Commissioner of Health on the 6th day of November, 1978, at 9:30 a.m. in Room 105, Minnesota Department of Health Building, 717 Delaware Street Southeast, Minneapolis, Minnesota 55440, after proper notice required by Minn. Stat. § 15.0412 was served upon all persons, associations and other interested groups registered with the Secretary of State for that purpose and following publication of the rules.

After affording interested persons an opportunity to present written and oral data, statements and arguments, and having heard and considered all of the testimony and evidence adduced and upon the records, files and proceedings herein, and applicable statutory standards or criteria, and having confirmed the need for and reasonableness of the above-captioned rules,

NOW, THEREFORE, IT IS ORDERED that these rules identified as 7 MCAR § 1.172 relating to tests of infants for inborn metabolic errors causing mental retardation are adopted this 19th day of January, 1979, pursuant to authority vested in me by Minn. Stat. §§ 144.125, 144.05(a), (b), and (c), 144.12 and 144.06 (1978).

STATE OF MINNESOTA

COMMISSIONER OF HEALTH



WARREN R. LAWSON, M.D.
Acting Commissioner

STATE OF MINNESOTA
OFFICE OF HEARING EXAMINERS
ROOM 300 – 1745 UNIVERSITY AVENUE
ST. PAUL, MINNESOTA 55104
(612) 296-6910

January 23, 1979

RECEIVED
JAN 25 1979
Attorney Generals Office
Health Division

Mr. Terry P. O'Brien
Special Assistant Attorney General
Minnesota Department of Health Bldg.
717 Delaware Street SE
Minneapolis, Minnesota 55440

Re: In the Matter of Proposed Amendments to 7 MCAR § 1.172 Relating to Tests of Infants for Inborn Metabolic Errors Causing Mental Retardation
HLTH-79-007-HC

Dear Mr. O'Brien:

Enclosed please find the Report of the Chief Hearing Examiner on the issue of substantial change pursuant to Minn. Stat. § 15.052, Subd. 3.

Yours very truly,

Duane R. Harves

DUANE R. HARVES
Chief Hearing Examiner

DRH:sh
Enc.

STATE OF MINNESOTA
OFFICE OF HEARING EXAMINERS

FOR THE DEPARTMENT OF HEALTH

IN THE MATTER OF THE PROPOSED)
AMENDMENTS TO 7 MCAR § 1.172)
RELATING TO TESTS OF INFANTS)
FOR INBORN METABOLIC ERRORS)
CAUSING MENTAL RETARDATION.)

REPORT OF THE
CHIEF HEARING EXAMINER

WHEREAS, a hearing was held on November 6, 1978, before Harry Seymour Crump, a Hearing Examiner of the State Office of Hearing Examiners, on the above-entitled matter in compliance with Minn. Stat. § 15.0412, Subd. 4; and

WHEREAS, the Report of Hearing Examiner made pursuant to Minn. Stat. § 15.052, Subd. 3, was issued to the Department of Health on December 14, 1978; and

WHEREAS, the Department of Health has now determined to adopt rules pursuant to Minn. Stat. § 15.0412, Subd. 4; and

WHEREAS, the Department of Health has submitted said rules to the Chief Hearing Examiner for review pursuant to Minn. Stat. § 15.052, Subd. 4, and Rule HE 110; and

WHEREAS, the Chief Hearing Examiner finds that the final proposed rules are not substantially different from those proposed at the public hearing and that the Department of Health has met all requirements of Minn. Stat. § 15.0412, Subd. 4.

NOW, THEREFORE, upon receipt of this Report, the Department of Health has the responsibility of submitting the complete hearing record and the rules as adopted by the Department to the Attorney General, notifying all persons who requested to be informed that the hearing record has been submitted to the Attorney General, and publishing in the State Register, all pursuant to Minn. Stat. § 15.0412, Subd. 4.

Dated this 23rd day
of January, 1979.

Duane R. Harves

DUANE R. HARVES
Chief Hearing Examiner