Welcome to the fourth issue of the Heel Stick News! We have made some changes to the publishing of the newsletter. It is now a biannual newsletter. We have added regular columns for the endocrine, metabolic, hemoglobinopathies, lab, and public health aspects of our INMSP program. We have also had some changes in our program. Beginning July 15, 2004 we will have a new Medical Director and Metabolic Geneticist. See page 5 for more information. This issue of the Heel Stick News will focus on biotinidase deficiency.

**Newborn Screening for Biotinidase Deficiency**

**Iowa Success Story**

Gage Blunt of Mason City, Iowa appeared healthy at birth. It came as a complete shock to his parents when they received a call that he had an abnormal newborn screen. His screen was presumptive positive for biotinidase deficiency, a disorder they had never even heard of before. They soon learned he was born just weeks after Iowa began a pilot to screen newborns for biotinidase deficiency. The more they learned about the disorder, the more worried they became. Additional testing eventually confirmed partial biotinidase deficiency. Fortunately, the complications of this disorder can be avoided with early diagnosis and treatment. Gage takes a biotin supplement twice each day and will continue to take it for the rest of his life.

Gage’s father, Shane Blunt says, “We feel blessed that they were able to pick this up through newborn screening. If Iowa hadn’t added biotinidase to the disorders they screen for, he may have gone undiagnosed for years. He would be at risk for serious complications. Because of his early diagnosis through newborn screening, he is healthy. He takes his biotin supplement twice a day and he is a normal, happy and healthy two year old. ”

Biotinidase deficiency is a rare but serious inherited disorder. Infants born with biotinidase deficiency lack an enzyme that normally allows the body to reuse the vitamin biotin. Biotin helps maintain normal body functioning. Symptoms of biotinidase deficiency include...
The ability to effectively screen, diagnose and treat biotinidase deficiency is the result of many years of research by Dr. Barry Wolf. Dr. Wolf first described biotinidase deficiency in 1983 and soon after developed a simple laboratory technique that would prove to be useful in screening for the disorder.

Two decades later, Dr. Wolf is considered to be the world expert on biotinidase deficiency. His research presently focuses on the genetic changes responsible for the clinical and biochemical features of the disorder. Dr. Wolf states in a recent publication, “there are many important and interesting questions about this disorder that must be addressed and answered. However, when compared with other inherited metabolic diseases, biotinidase deficiency is still one of the most readily treatable. If a child must have an inborn error of metabolism, let it be biotinidase deficiency and let it be identified by newborn screening.”

Since Dr. Wolf and his colleagues developed the screening methodology, 30 state newborn screening programs have embraced universal screening for biotinidase deficiency.

The March of Dimes recommends that every baby born in the United States receive biotinidase deficiency screening. Since Iowa began testing newborns for the disorder, six individuals have been confirmed with biotinidase deficiency, including one sibling diagnosed.

Interferences with biotinidase testing may include the following:

- Transfusion
- Prematurity/low birth weight
- Improper collection, drying, or handling of collected specimens
- Exposure of specimens to heat and humidity
- Delayed submission of specimens to the testing laboratory

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seizures, low muscle tone, developmental delay, hearing loss, mental retardation, optic atrophy, laryngeal stridor, ketolactic acidosis and recurrent infections. The onset of symptoms occurs anywhere from two weeks to two years of age. This disorder occurs in about 1 in every 60,000 births.

The good news is that biotinidase deficiency is treatable with a biotin supplement. In addition, most of the symptoms are preventable through early detection and management. All babies born in Iowa after March 1, 2002 have been screened for biotinidase deficiency.

Biotinidase Deficiency Web Sites

- eMedicine.com
  Web site: www.emedicine.com/PED/topic239.htm
- Family Support Group
  Web site: www.geocities.com/biotinidasedeficiency/
- Gene Clinics
  Web site: www.geneclinics.org/profiles/bicotin/

A Newborn Screening Champion

Tonya Diehn, State Coordinator for Genetic Services

The ability to effectively screen, diagnose and treat biotinidase deficiency is the result of many years of research by Dr. Barry Wolf. Dr. Wolf first described biotinidase deficiency in 1983 and soon after developed a simple laboratory technique that would prove to be useful in screening for the disorder.

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Fundamental Testing in Biotinidase

Laurie Hazelwood, Iowa Neonatal Metabolic Screening Laboratory

The INMSP laboratory uses a simple colorimetric method to determine the presence or absence of the enzyme biotinidase in a punched blood spot sample. Specimens are punched into microtiter trays, a substrate is added, and the trays are incubated overnight. If biotinidase is present, the enzyme will cleave the amide bond of the provided substrate, biotinyl-p-aminobenzate (B-pABA), leaving free biotin and p-aminobenzoate (p-ABA). The p-ABA is then diazotized and a naphthol reagent is added, producing a purple-colored solution. If a sample lacks biotinidase, the p-ABA cannot be liberated from the substrate, and color development will not occur.

Lab staff visually compares color development of the test samples to known controls, which range from a lack of color (straw-colored) to increasing intensities of purple. A sample with very weak color or no color development is repeated in duplicate. If results again show no enzyme activity or very reduced activity, the sample is reported as Presumptive Positive for biotinidase. Samples with an adequate purple color (enzyme present) are reported as Within Normal Limits.

Info from the Center

As of May 31, 2004 the Center is looking for a new state coordinator. Tonya Diehn has decided to continue her education. She has worked with the state of Iowa for the past four years and leaves many friends as she pursues her new adventure. We wish Tonya the best of luck as she spends the summer with her boys and begins a new chapter in her life.

We would like to highlight one of the Center’s free tools available for your neonatal metabolic screening program. It is the INMSP Healthcare Practitioner’s Manual —This is a guide created to help the health care practitioner comply with Iowa rules and to better understand the Iowa Neonatal Metabolic Screening Program (INMSP). The manual includes information on specimen collection, when to obtain a second sample, frequently asked questions, definitions of each disorder, treatment, outcome, sample screening reports, additional resources, and much more. To view or print a copy of the manual go to our web site at www.idph.state.ia.us/genetics.

Humidity Issues in the Lab

How it Affects the Biotinidase Samples

Laurie Hazelwood, Iowa Neonatal Metabolic Screening Laboratory

During the summer months, the newborn screening laboratory has noticed a higher incidence of false positive results for the biotinidase screen. The enzyme botinidase may degrade if exposed to high heat and humidity after collection or during sample transport, which may result in reduced or no enzyme activity.

Last summer several presumptive positive biotinidase results were reported to one facility in particular. INMSP learned that their laboratory had been having problems with humidity control, and the problem was remedied over time. Since specimens are transported to INMSP by the postal service, some environmental exposure to heat and humidity during the summer months cannot be avoided. But by maintaining proper drying conditions, and by promptly mailing specimens to the screening lab, submitters can reduce the likelihood of false positive biotinidase results.
New Retention Policy for INMSP

A new policy for purpose, storage, and use of specimens residual to those collected for INMSP will be implemented by the Iowa Neonatal Metabolic Screening Program (INMSP). The new policy addresses the definition of residual newborn metabolic screening specimens, stewardship, storage conditions, notice of storage of specimens to parents, validation of specimen integrity for specified analytes at defined time periods, access to residual specimens for specific diagnostic/clinical, quality assurance/improvement and research purposes and standard operating procedures for inclusion to, monitoring of, and retrieval from the specimen repository.

What is a residual specimen?
A residual newborn metabolic screening specimen is defined as the portion of the dried blood spots leftover after the completed newborn screening services of the INMSP. The INMSP collection form consists of dried blood spots on filter paper and baby and birthing center information.

Why are specimens retained?
Specimens are retained for several reasons:
1. Legal Accountability
   a. To confirm the existence of a specimen and its adequate collection
   b. Reconfirm newborn screening analytical results
   c. Allow for retesting of a specimen when a child has been subsequently diagnosed with a screenable disorder
2. Laboratory Quality Assurance/Improvement
   a. Necessary for laboratory to perform continuous quality assurance and improvement of testing methodologies
3. New Method Evaluations and Comparisons
   a. Necessary for laboratory to compare testing methodologies
   b. Necessary for laboratory to develop and validate new testing methodologies
4. Diagnostic/clinical purposes
   a. Availability of a specimen for diagnostic purposes in the event of an unexplained infant death or SIDS death. Definitive diagnosis is beneficial for counseling families and providing risk assessment for future pregnancies.
   b. Availability of a specimen when parent requests additional testing.
5. Epidemiological research to benefit the public health
   a. Permit the conduction of population studies on anonymized specimens to determine the incidence and prevalence of biochemical markers and/or genetic polymorphisms for disorders and diseases. An anonymized specimen is defined as one, which cannot be traced back to or linked with the particular infant from whom the specimen was obtained.
6. Basic health-related research
   a. Permit the conduction of individualized studies on anonymized and identifiable specimens to advance medical knowledge on birth defects, disorders and disease. (Informed consent is required.)

How long will the specimens be retained?
Specimens shall be retained for a minimum of five years. The specimens shall be retained for one year at –70° C and then archived for four additional years at room temperature.

When will this policy be effective?
The new policy for purpose, storage, and use of specimens residual to those collected for INMSP will be implemented January 1, 2005.
**Hemoglobinopathy Highlights**

Did you know…………………….. that the Hemoglobinopathy Program is starting to do Transcranial Doppler (TCD) Ultrasounds with their Sickle Cell Patients.

There is new information to suggest that children with sickle cell disease may benefit if we could predict who is at risk for a central nervous system stroke. A study published in the July 1998 issue of the New England Journal of Medicine showed that patients who went on a transfusion protocol (based on abnormal findings on the TCD) had a decreased risk of stroke.

If a patient (age 2-16) has an abnormal TCD ultrasound, another ultrasound is repeated in four to six weeks. If abnormal a second time, then the patient may be started on a chronic transfusion program in hopes of decreasing the risk of having a stroke.

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**July 2004: New Geneticist in Iowa**

The INMSP family is growing! In July, Dr. Sara Copeland will be joining the program as the chief metabolic consultant and new medical director.

Sara is a pediatrician and a metabolic geneticist. She is the author of 26 metabolic disorder fact sheets. Sara is interested in the long-term outcomes of infants identified through newborn screening with inborn errors of metabolism detectable by tandem mass spectrometry. She is a lead investigator on a Centers for Disease Control and Prevention funded grant looking at diagnosed infants in Iowa, Oregon and Idaho.

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**Notes from Endocrine**

The follow-up staff strive to ensure that abnormal newborn screen results are addressed in a timely manner. The following is a list of items that may lead to a delay in the follow-up of these results. Do you recognize any items that you may be able to address in your own practice?

- The newborn screen collection form is not accurate, complete, or legible.
- The baby’s weight or physician name is omitted from the form.
- When the physician name is listed, it is actually the mother’s obstetrician or the on-call physician present at the baby’s birth and not the primary-care provider.
- Occasionally, initials are entered onto the form instead of the physician’s surname.
- The baby’s parent has no phone, does not speak English, or has moved out of the area.
- The baby does not have a primary health-care practitioner.
- The baby was adopted or placed into foster care.
- The baby’s last name has changed from the name identified on the initial newborn screening form.
What You Need to Know

The 80th General Session of the Iowa legislative session passed House File 2362 which revised Iowa Code Chapter 136A “The Birth Defects Institute”. This chapter within the Iowa Code had not been revised for 20 years. The changes reflect the activities conducted by the Birth Defects Institute. The code revision included the renaming of the Birth Defects Institute to the Center for Congenital and Inherited Disorders. Concerned parents and legislators who did not like the stigma given by the “Birth Defects Institute” initiated the name change. The effective date for the Iowa Code revisions was July 1, 2004.

Due to the changes in the Iowa Code, we are currently in the process of revising our Administrative Rules 641 Chapter 4. Chapter 4 details the activities and responsibilities of the INMSP program as well as the responsibilities of health-care providers, birthing hospitals, birthing centers, or laboratories in complying with the program’s function and activities. The proposed changes provides additional definitions and clarification on confidentiality in the INMSP program. It also modifies the neonatal metabolic screening specimen retention policy (see page 4 for more information.) The changes model the INMSP program after the early hearing detection and intervention screening rules. The Chapter 4 rule changes are proposed to become effective September 2004.

www.idph.state.ia.us/genetics

Visit the Center for Congenital and Inherited Disorders web site. It is full of information for health professionals, parents, and consumers. See the NEW! folic acid section on the website!

Metabolic Matters.....

We are pleased to announce the formation of Iowa’s first non-profit organization for children, teens, and adults with PKU as well as the parents, relatives, and friends who support them. PKU in its “classic” form, is a rare, inherited metabolic disease that results in mental retardation and other neurological problems when treatment is not started within the first few weeks of life. When a very strict diet (including a necessary synthetic formula) is begun early and well-maintained, affected children can expect normal development and a normal life span. Excess phenylalanine is toxic to the central nervous system and causes the severe problems normally associated with PKU.

The diet for the most severe form of PKU eliminates all of the very high protein foods since all protein contains phenylalanine. Except in rare circumstances, the diet does not allow consumption of meat, fish, poultry, milk, eggs, cheese, ice cream, legumes, nuts, or many products containing regular flour. A synthetic formula is used as a nutritional substitute for the eliminated foods to provide the protein needed for growth.

The Iowa PKU Foundation was founded on May 15, 2004, as a source of emotional, educational, and financial support for PKU patients and their families. The first priority is to mandate formula coverage for all Iowans. In addition, they would like to set up a college scholarship fund for PKU teens. Please contact Blythe Stanfel (blythe.stanfel@mchsi.com), if you have any questions or if you would like to contribute to the success of the Iowa PKU Foundation.
The Laboratory Log

An educational inservice on newborn screening collection procedures was held at the University of Iowa Hospitals and Clinics at three different times (in an effort to accommodate different work schedules) throughout the day on March 10, 2004. There were many employees that attended with a variety of lab experience. The session was well received and participants asked excellent questions.

Are you new to the field of newborn screening collection or would you benefit from a refresher course in proper collection procedures? The University Hygienic Laboratory staff are offering an educational in-service that will take you through the entire newborn screening collection process. Some of you may remember an in-service entitled, “Doing It Right the First Time”, that was provided last year through ICN. This educational opportunity is a shortened version. The educational in-service will cover the following:

§ Disorders screened by the program
§ Importance of parent education
§ Neonatal metabolic screening considerations
§ Proper collection procedures
  Filling out the collection form
  How to collect an acceptable neonatal metabolic screening specimen
  Reasons for which specimens are rejected
  Simple spot check
§ Iowa Neonatal Screening Laboratory
§ INMSP Screening Reports
§ Questions and Answers

If you are interested in borrowing the video for in-house training or to schedule this educational in-service, please call (515) 243-0141 and ask for Marcia Valbracht.

Questions regarding Iowa biotinidase deficiency screening....

may be directed to the following persons:

Follow-up and treatment questions:  
(800) 260-2065  
University of Iowa Department of Pediatrics  
Judy Miller, ARNP  
Metabolic Clinic Coordinator  
judith-miller@uiowa.edu

or  
Val Sheffield, M.D., Ph.D.  
Director, Division of Medical Genetics  
val-sheffield@uiowa.edu

Laboratory questions:  
515-243-0141 or 319-335-4500  
University Hygienic Laboratory  
Stan Berberich, Ph.D  
sberberi@uhl.uiowa.edu

Suggestions or Ideas Wanted

Since we would like to provide our readers with a wide range of information about activities of the Iowa Neonatal Metabolic Screening Program, we invite you to submit ideas for future articles. If you have any comments, or would like to make a contribution, please contact Dawn Mouw, dawn.mouw@idph.state.ia.us. If you would like to view the newsletter archives, please use our web site: www.idph.state.ia.us/genetics.
Iowa Newborn Hearing Screening

The Iowa Newborn Hearing Screening Legislation, was signed on May 1, 2003 by Governor Vilsack. This means that as of January 1, 2004 every newborn in Iowa is to be screened for hearing loss. Babies born in hospitals must be screened prior to discharge from the birthing hospital where they delivered. The bill also mandates that the results of the screen, re-screens, and diagnostic assessments for children under age three be submitted to the Iowa Department of Public Health for follow-up. The bill allows for parents to deny the screening with a written refusal. Iowa is the 38th state to pass Newborn Hearing Screening Legislation.

How common is congenital hearing loss?
According to the National Center for Hearing Assessment and Management, 3 of every 1000 newborns have a hearing loss, making it the most frequently occurring birth defect in the United States. About 37,000 babies are born each year in Iowa. Of these, more than 90 will have a hearing loss. Most babies born with a hearing loss are born to parents with normal hearing.

Why screen a baby so early?
Because time is of the essence. Research shows that it is imperative to identify and treat a hearing loss by the time a baby is 6 months old, in order to prevent delayed communication development. The earlier a child is identified, the earlier an intervention can be implemented, and the greater the chances are that the child will develop communication and social skills at the same rate as his/her peers. Not only will early intervention help with a child’s speech and language skills, but it will also increase a child’s self-esteem and decrease costs of needing special education services due to late identification of the problem.

Is the newborn hearing screening conducted as part of the INMSP program?
No, the newborn hearing screening program is a separate program that has its own protocol and forms that need to be completed. In Iowa, babies will have an AABR screen or an OAE screen before leaving the hospital.

The auditory brainstem evoked response system (AABR), is where the screener tapes electrodes to the baby’s forehead and behind each ear, puts earphones on the baby, and then plays a soft clicking sound that stimulates the baby’s hearing nerves. None of this hurts the baby! The electrodes then measure the baby’s response to these soft clicks.

The automatic otoacoustic emissions system (OAE), is where the screener places a small, soft earphone in each of the baby’s ears, one at a time. The screening equipment plays quiet sounds and measures the ear’s response. The test is performed while the baby sleeps comfortably.

If the baby fails the newborn hearing screening, does that mean he or she has permanent hearing loss?
Not necessarily. Many babies who do not pass the newborn hearing screen turn out to have normal hearing. On the other hand, some newborns who pass the hearing screening may develop hearing problems later. It is important to encourage parents to get their children re-screened if they previously failed the newborn hearing screen. It is also important to observe children’s communication abilities as they grow to identify if they have developed a late-onset hearing loss.