C A R E S FOUNDATION Inc.

Congenital Adrenal hyperplasia Research, Education & Support

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Volume 1
Issue 3
Fall 2002

The Research Issue - Part 1

In this Issue

"It's the Most Wonderful Time of the Year.."

Managing CAH in public schools

With the beginning of school come thoughts of how to successfully manage our CAH kids in a public school. While this might be a source of stress for parents just entering the school system, rest assured that as time passes, you'll get into the groove a better, stronger parent. Managing CAH in the schools is a partnership between you, the teacher, and the administration (school nurse, if available and the principal). Here are a few pointers to help those parents about to send off their precious CAH child. (Private institutions can carry their own set of rules. However, hopefully some of these ideas can help those of you choosing private schooling.)

1. ***Meet with the school nurse (or person in charge of medication administration).*** Discuss CAH with the people who will be caring for your child on a daily basis. Try to convey the seriousness of the condition without too much drama. This approach might seem a bit overwhelming for some educators.

2. ***Find out what is required in your area concerning daily medication requirements.*** A doctor's order is generally required detailing the time, dose, reason for medication (diagnosis of disorder), side effects, if any, etc. Many times it will require the doctor's signature AND the parent's authorization. These requirements vary not only from state-to-state, but from county-to-county, etc. Some jurisdictions are extremely rigid whereas some are more flexible. ***Please note:*** A separate doctor's order might be required for medication administration outside of the daily dose. This is called a PRN (Latin for 'as needed') and simply covers for medication to be given under other circumstances. This could include if you have (GASP!) forgotten the morning meds and you'd like the school to administer them, if your child has had a serious injury during the school day and you'd like Cortef to be administered orally, if your child develops a high fever during the school day and you'd like extra Cortef to be administered orally. A PRN will usually include wording such as, "to be administered in times of injury, fever, and/or

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CAH Family Support Groups Around the Country

ALABAMA
Contact Susan Davenport
205-665-1934
susand@sepcousa.com

ARIZONA
Fall Family Picnic
Saturday, October 26, 2002
Contact Michelle May
480-759-0870
michlmay@aol.com

TEXAS
Contact Sandra Billings
281-861-6043
billprop1@msn.com

WISCONSIN
Contact Lisa Jaskie
(414) 645-0782
lisa1273@msn.com

Save the Date!!

CAH Family Workshop

Johns Hopkins University Hospital
Baltimore, Maryland
March 8, 2003
1:00-6:00 PM

Featured Guest Speakers

DR. CLAUDE MIGEON, Johns Hopkins
DR. DEBORAH MERKE, NIH
DR. SHERI BERENBAUM, Penn State Univ.

More information to come. Check our website for updates. An email alert will be sent out as soon as detailed information is available.

A Message from the Executive Director:

Dear Friends,

CARES Foundation has been busy these last few months in its quest to service the concerns of the CAH community. This past March, leading international experts in CAH met to draw up guidelines to improve medical care for CAH patients. I wrote an extensive memo to the chairs of the conference outlining the issues that I felt deserved attention. I am pleased to say that most of these issues were addressed. The conference produced a CAH Consensus Statement which will help to provide consistent standards of care for our community and hopefully improve care for all affected by the disease. My summary of the Statement is on page 3.

Encouraging CAH research and advocating for increased federal funding is a major goal of CARES Foundation. We invited several experts who are engaging in CAH related research to summarize their work in our newsletter. The response has been so tremendous that this topic will continue into the next newsletter. It is encouraging to me, as a parent, to know that so much research is ongoing. However, there is much more work to be done. We must strive, as a community, to ensure that CAH receives adequate research funding and to urge the medical profession to continue its focus on CAH.

In April, I went to Houston, Texas for our first CAH Family Workshop and was delighted to meet so many of our families. Drs. Sheila Gunn, Maria New and Sheri Berenbaum spoke to approximately 70 attendees. I am extremely grateful to the doctors who spoke and the staff at Texas Children's Hospital who sponsored the event. But, most of all, I must thank Sandra Billings--without her hard work and dedication to this event, it could not have happened. Sandra—you're the best! Thank you!

In May, I was invited to attend Dr. Maria New's conference in Tempe, Arizona on the *Genetic Basis of Sexual Differentiation Disorders*. The conference was very enlightening. I was especially pleased to see that those involved in the medical management of virilized CAH infants are attempting to deal with some of the issues voiced by the adult female CAH population in their clinical practices. While in Arizona, I got to attend the first meeting of the Arizona CAH support group. What a wonderful group of families! They have some fun activities planned including a Family Picnic on October 26th (see page 1 for details).

We are continuing our fight to ensure that every child born in the US and abroad is screened for CAH at birth. In July, I had the opportunity to meet with the Chief Policy Advisor for the Bill Simon for Governor campaign in California. Since we have had such difficulty in gaining support for CAH newborn screening under the current administration, I was hopeful that this issue would fall on sympathetic ears in the opposition. In fact, the campaign was unfamiliar with the issue and was very grateful to us for bringing it to their attention. They are indeed focused on children's healthcare in the state, and I am quite hopeful that Bill Simon will quickly address the CAH newborn screening if elected in California.

This summer, some of our Ohio families wrote letters in support of CAH newborn screening. Their efforts have paid off! Ohio's newborn screening committee will be meeting in October and CAH is the first issue on the agenda. The state purchased the necessary machinery earlier this month and they expect to begin CAH screening sometime in 2003! Thanks Ohio families!

We have another CAH family Workshop planned for March 8th, 2003 in Baltimore, Maryland sponsored by Johns Hopkins. Please save the date! I hope you enjoy this issue of our newsletter!

Warm Regards,

Kelly

Summary of The CAH Consensus Statement of the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology

From the Journal of Clinical Endocrinology and Metabolism 87(9):4048-4053 September 2002

This past March 2002, 40 physicians, psychologists, scientists, and surgeons from countries in North America, Europe, Japan and Australia met in Gloucester, Massachusetts to discuss the management of congenital adrenal hyperplasia (21-OHD) and to develop a set of universal guidelines. The group recognized the difficulty in managing CAH, despite over 50 years of experience with steroid replacement therapy as well as the substantial variation in clinical practice. The highlights of the guidelines are as follows:

Neonatal Diagnosis, Treatment and Clinical Evaluation

The Group recommended that all babies suspected of having congenital adrenal hyperplasia (CAH), whether through adrenal crisis or symptoms, virilized genitalia or an abnormal newborn screening result, the infants should receive immediate expert medical attention and evaluation by a pediatric endocrinologist. Further, "[a] well-organized multidisciplinary team (including specialists in pediatric endocrinology, psychosocial services, pediatric surgery/urology, and genetics) is essential for the diagnosis and management of the infant with ambiguous genitalia. It is important that the coordinator of the team has experience in the long-term care of the patient with CAH and provides a consistent message to the parents." A comprehensive evaluation of the infant suspected of having CAH should be made, including "a complete history, a physical examination, a reliable ultrasound investigation of the internal genitalia and adrenals, karyotype or fluorescence in situ hybridization for sex chromosome material, and a rapid, reliable plasma or serum measurement of 17OHP. Premature newborns may need serial measurements of 17OHP to differentiate false positive results from affected infants with CAH."

Newborn Screening For CAH

The group found newborn screening for CAH to be "beneficial and recommended". The report states that CAH newborn screening is sensitive enough to detect almost all classical and some non-classical CAH affected infants. The report goes on to set forth the parameters and methodology recommended for laboratories conducting CAH newborn screening. With respect to DNA analysis, it states that such testing is not essential, but may be helpful to the diagnosis and in genetic counseling. The genetic defects may not always correspond to the clinical manifestations of the disorder. The DNA of the parents is required for best results when conducting DNA testing of children.

Prenatal Treatment and Diagnosis

The report states "[p]renatal treatment has been advocated for fetuses at risk for classic CAH but is not appropriate for nonclassic CAH." While still considered somewhat controversial, current medical research has shown that "very early institution of treatment ameliorates the genital virilization in all affected females and completely eliminates it in more than 85%." Therapy must begin earlier than 9 weeks after the last period. The group also sets forth specific inclusion criteria for prenatal treatment and gives the dosage formula. The group states, "[n]o consistent untoward effects have been reported, and birth weight is not reduced. However, few treated fetuses have reached adulthood, and long-term prospective studies have not been done. Thus, all agree that the results to date are very good, but long-term safety has not yet been proven in patients treated to term or in the 7 of 8 fetuses in whom treatment is stopped because they are male or unaffected." The side effects for treated mothers include edema, weight gain and stretch marks, but no increased risk for gestational diabetes or hypertension has been shown. The group clearly states, however, that prenatal treatment should not be undertaken by general obstetricians in the community. Such treatment requires a level of expertise and should be monitored by a team including, "a pediatric endocrinologist, an expert in high-risk obstetrics, a genetic counselor, and a reliable molecular genetics laboratory." Specialized teams should be designated using approved protocols and subject to reviews boards in recognized centers only. Parents must give written informed consent to prenatal treatment after reviewing the benefits and risks. The group states that further long-term follow-up studies are recommended.

Surgical Management and

(Continued on page 4)

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This newsletter is published 3 times a

CAH Consensus Statement

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Psychological Issues

Decisions about genital surgery should only be made "after complete disclosure of all relevant clinical information and all available options have been discussed and after informed consent has been obtained." The report sets forth the goals of surgery and describes the degree of virilization of the female infant that warrants a recommendation of surgical intervention. It notes that lesser degrees of virilization may not warrant surgery. "Surgery to reduce clitoral size requires careful consideration." The group recommends that any such surgery be done when the infant is between the ages of 2-6 months because surgery is technically easier than when the child is older. "The early operation should be a one-stage complete repair using the newest techniques of vaginoplasty, clitoral, and labial surgery [....] and should be carried out at a center with experience of at least 3–4 cases/yr. Revision vaginoplasty is often required at adolescence, and the timing should be decided with the patient and family." The group does not recommend surgery between the ages of 12 months and adolescence absent complications with specific medical problems. Vaginal dilatations should not be done in childhood and genital examinations should be minimized. Genital photography is discouraged. These designated centers for genital reconstruction should have one surgical team responsible for all CAH reconstruction. Outcomes should be audited. The group acknowledged concerns about early surgery, but stated that surgical techniques have improved and cautioned against judging outcomes from outdated procedures.

The report notes that females with CAH often show behavioral masculinization, "most pronounced in gender role behavior, less so in sexual orientation, and rarely in gender identity". The group concludes that, with respect to Prader 5 (extremely virilized) CAH female infants, there is insufficient evidence to support a sex assignment of male. The group indicates that optimism is warranted for the outcome of CAH females who undergo surgery using current techniques and skilled surgeons. The group pointed to the importance of professional psychological services and support groups for affected individuals and their families. The group concluded that, "[a]s the pace of societal change, including the flexibility of gender role, increases, more frequent review of management policies and long-term outcomes is important."

Treatment Considerations

CLASSICAL CAH

The report sets forth a dosing schedule for physicians to follow and recommends hydrocortisone in tablets (divided or crushed) for infants and children. The group cautions against use of hydrocortisone oral suspensions and against excessive doses. "Excessive doses, especially during infancy, may cause persistent growth suppression, obesity, and other Cushingoid features. Therefore, complete adrenal suppression should be avoided."Long-acting glucocorticoids may be an option after a child has finished growing. The group recommends prednisolone over prednisone and gives dosing amounts for physicians and recommended tests for monitoring patients. The group states that all classical CAH infants at diagnosis be treated with fludrocortisone. The report gives dosing requirements for this medication as well as for sodium chloride supplements. The report also recommends the frequent monitoring for children and sets forth the tests that should be conducted during the office visits. It also notes, "Patients receiving adequate replacement therapy may have hormone levels above the normal range."

NONCLASSICAL CAH

"The standard method of diagnosis involves a 60-min stimulation test with (1–24)ACTH. However, a single early-morning (before 0800 h) level of 17OHP may also serve as a fairly reliable screening tool." The group recommends treatment only for those patients with nonclassical CAH who experience symptoms of the disorder.

STRESS DOSING

"Patients with CAH should carry medical identification and information concerning therapy for stress. Caregivers should have an emergency supply of IM [intramuscular] HC or glucocorticoid suppositories." Patients should be given stress doses of hydrocortisone during illness with fever over 101F, when vomiting or when unable to take food by mouth, after serious injury and before any surgery. While engaging in endurance sports may require extra medication, mental and emotional stress does not. The stress dose is 2-3 times the regular glucocorticoids dose. The report also gives dosages for intravenous infusions of hydrocortisone for surgery, trauma or adrenal crisis.

Management of CAH and NCCAH

Genital examinations should be avoided absent specific clinical necessity. Psychological support and evaluations of the teenage patient and

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CAH Consensus Statement

(Continued from page 4)

her family "should be a routine component of the comprehensive care and management of these patients.... Counseling regarding sexual function, future surgeries, gender role, and issues related to living with a chronic disorder should be addressed."

THE ADOLESCENT PATIENT

When care is transferred from the pediatric endocrinologists to an adult endocrinologist, the group recommends that, "a transition team should also include, as needed, a gynecologist, a urologist, and a psychologist with specific expertise and interest in the treatment of such patients." Adult and adolescent males need to be informed of the necessity of compliance with treatment to enhance fertility and reduce the risk of nodules in the testes, and of the importance of for frequent self-examination of the testes for nodules. Surgical removal of these masses may be necessary to preserve or improve fertility. Adult and adolescent females need to be assessed for the effectiveness of genital repair and vaginal stenosis should be addressed. Psychological counseling should be a part of management of these patients. Fertility issues should be addressed with nonclassical patients. "The risk of women with CAH or NCCAH having an affected fetus is low."

THE PREGNANT CAH WOMAN

The pregnant CAH/NCCAH woman should be cared for in a tertiary center with experience and equipment to handle such pregnancies. The patient should be treated with glucocorticoids that do not cross the placenta, such as hydrocortisone and prednisolone, and dexamethasone (which crosses the placenta) should be avoided. Dexamethasone in the pregnant CAH/NCCAH patient is only appropriate when used in prenatal therapy. In classical CAH women who have undergone reconstructive surgery, elective cesarean section is recommended to avoid damaging the genital area. Hydrocortisone will need to be increased during cesarean section surgery and a pediatrician should be present to care for the newborn and to begin diagnosis and treatment if an affected infant is expected.

Experimental Therapies and Future Developments

Adenalectomy should only be considered when conventional therapy is failing and long-term follow-up can be secured. This therapy requires life-long monitoring and vigilance in administering medication.

CRH antagonists for adrenal suppression holds promise but needs further study.

Antiandrogens and aromatase inhibitors used with hydrocortisone and fludrocortisone have shown some benefit in short-term studies. However, no long-term safety data is available and liver function must be monitored carefully.

Epinephrine ("adrenaline" the flight/fright hormone) deficiency in CAH may play a role in responsiveness to stress. This is being studied now for possible therapeutic implications.

Preimplantation genetic diagnosis has been done in a single published case, and gene therapy is being investigated in a mouse model of the disease, but neither is available for common use in humans.

DHEA replacement is being studied in Addison's patients, but it is unclear whether this holds any relevance to CAH.

11 beta-HSD inhibitors are not recommended, but may have potential to decrease the dose of glucocorticoids (i.e., hydrocortisone) needed for treatment.

Growth hormone combined with depot leuprolide acetate (Lupron) treatment has been studied in a small group of short CAH patients. Growth rate and final predicted height (which is not the same as actual final height) significantly improved, but the adult heights are not yet available.

CARES Foundation wishes to thank the participants at this conference for tackling these important issues in the management and care of CAH/NCCAH patients. We encourage this group to convene regularly to continue the discussion of these important issues and to attempt to provide further guidance to their colleagues in the field. The benefits to the CAH community will be far reaching and hopefully will lead to a higher and more consistent standard of care for those affected. Moreover, we wish to thank Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology for sponsoring this conference.

The participants were: *Sheri Berenbaum (PA), George Chrousos (MD), Peter Clayton (UK), Gordon Cutler (IN), Sabine De Muinck Keizer-Schrama (The Netherlands), Patricia K. Donahoe (MA), Patricia A. Donahoue (IA), Malcolm Donaldson (UK), Maguelone Forest (France), Kenji Fujieda (Japan), Lucia Ghionizz (Italy), Maria Ginalska-Malinowska (Poland), Melvin M. Grumbach (CA), Annette Grüters (Germany), Kerstin Hagenfeldt (Sweden), Raymond L. Hintz (CA), John W. Honour (UK), Ieuan A. Hughes (UK), Ursula Kuhnle-Krahl (Germany), Peter A. Lee (PA), Heino Meyer-Bahlburg*

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Newborn Screening Update

SENATOR DODD INTRODUCES BILL to ENCOURAGE NEWBORN SCREENING for LIFE-THREATENING DISORDERS

Press Release – August 28, 2002

Washington, D.C. - In an effort to protect newborn children from severe disability or death as a result of genetic, metabolic, or congenital disorders, Senator Chris Dodd, D-Conn., recently introduced legislation to help educate parents and health professionals about the critical importance of newborn screening. The Newborn Screening Saves Lives Act of 2002, S. 2890, seeks to resolve tremendous disparities among state screening programs through education, training, and outreach, and would also provide Federal support for follow-up care for children born with these diseases.

"A child's health shouldn't be influenced by a line drawn on a map," said Dodd. "Newborn screening is a valuable tool in efforts to treat children's health problems, and - as such - we need to ensure that every family and every health provider all across America has access to information about this critical resource. This is one test where failing shouldn't be an option."

Each year, over four million infants have blood taken from their heels to detect congenital conditions such as L-CHAD, a disorder that prevents the body from turning fat into energy, and sickle-cell diseases. As a result, approximately 1,000 infants each year are diagnosed with one of these disorders and can therefore receive treatment to help protect their lives and long-term health. However, each year more than 2,000 babies are estimated to be born with potentially detectable disorders that go undiagnosed because they are not screened - placing them at risk of disability or death from a condition which could have been treated had it been detected immediately after birth.

The Newborn Screening Saves Lives Act seeks to address the shocking lack of information available to health care professionals and parents about newborn screening. The bill would authorize grants to provide education and training to health care professionals, state laboratory personnel, families, and consumer advocates. The bill would also provide funds for grants to develop a coordinated system of follow-up care for those children diagnosed with a disorder detected through newborn screening, and would supplement ongoing efforts to establish national recommendations for newborn screening programs.

Although recent advances in medical technology have made it possible to screen for at least thirty genetic and metabolic disorders, states often lack the resources or the equipment to conduct a full battery of tests. Only Connecticut and Massachusetts screen children for thirty disorders; the vast majority of states test for eight or fewer. Many health care professionals, and many more parents, are unaware of the possibility of screening for disorders beyond those required by their state.

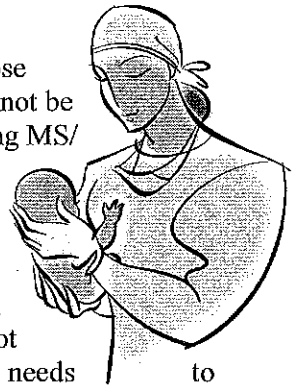
Earlier this year, Senator Dodd, who chairs the Senate Subcommittee on Children and Families, joined with Senator Mike DeWine (R-Ohio) to write a letter to the General Accounting Office (GAO) calling for a study of each state's newborn screening programs. The letter requested the GAO to report on individual states' efforts; how they test for disorders; the coordination among families, physicians, and laboratories involved; and the procedures and quality of data. The letter also requested a report on how states protect the privacy of this sensitive and critical health information. In June, Senator Dodd chaired a hearing of the Subcommittee on Children and Families, which received testimony on this issue from administration officials, parents, and health care professionals.

Newborn Screening in the States: Update

Our efforts in Ohio seem to be paying off. On Friday, October 25th, the Ohio Newborn Screening Advisory Committee will be meeting to discuss the implementation plan for CAH newborn screening. The State has already purchased the instruments needed to do the testing and have included the cost in the new kit fee. However, it is not set in stone. So, Ohio Families—if you can attend this meeting, you can help to ensure that this testing does indeed get added promptly to the program. The meeting is at the Quest Business Center, 8405 Pulsar Place, Columbus. The meeting is open to the public.

Oregon will be adding CAH to its screening program in January, 2003 and New York should begin CAH screening this month.

Utah needs our help now! They are looking at expanding their newborn screening program, but only to include those diseases that can be screened using Tandem Mass Spectrometry (MS/MS). CAH cannot be screened for with this equipment, so it will not be added at this time. CARES has written to V. Fan Tait, M.D., Director of CSHCN, Utah Department of Health, 44 North Medical Drive, Salt Lake City, Utah 84113 urging Utah to implement a comprehensive newborn screening expansion that also includes those diseases that cannot be screened for using MS/MS such as CAH. We strongly urge our families to write to Dr. Tait, even if you do not live in Utah. She needs to hear from families who have experienced the devastation and trauma of having a child with CAH detected late. Please help if you can.



Rare Disease Legislation Alert

On October 1, 2002, two critically important laws were passed in the House of Representatives that propose to strengthen research programs on rare disorders at the National Institutes of Health (NIH), and the Food & Drug Administration (FDA). The two bills are companion legislation for the *Rare Diseases Act of 2001* (S.1379), which was introduced in the Senate on August 3, 2001, by Senators Edward Kennedy (D-MA) and Orrin Hatch (R-UT). The House bills separate the two initiatives for the NIH and the FDA by making each a separate piece of legislation.

One bill in the House of Representatives is named *The Rare Diseases Act of 2002* (H.R. 4013). It will establish an official **Office of Rare Diseases** at the NIH. The Office will promote and coordinate research on rare disorders, and will create academic Centers of Excellence for research on these conditions. The NIH Office of Rare Desease would receive $24 million per year for this program.

The second bill in the House is named *The Rare Disease Orphan Product Development Act of 2002* (H.R. 4014). The law would provide $25 million per year for the **FDA's Orphan Products Research Grant Program**, which supports clinical trials of new orphan drugs, diagnostics, medical devices and medical foods. This program received only $12 million from Congress this year, which is less than the funds appropriated for these research grants in 1995. To date, 27 new products (24 orphan drugs and 3 medical devices) have been developed, and are currently on the American market because academic scientists and small companies received grants from this program to support their clinical trials.

Action Needed

The two bills are critically important to people with orphan diseases (such as CAH) who are waiting for new treatments and cures to be develop for their health conditions. In order to ensure that Congress will enact these important laws, interested people are urged to contact their U.S. Senators and **ASK THEM TO CO-SPONSOR S.1379. If we want these laws to be enacted this year, this must occur before Congress recesses before the election season this autumn.**

Please contact your Senators by phone either at his or her state office, or at their Washington, DC offices (phone the Capitol switchboard at

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"Your Child and Congenital Adrenal Hyperplasia"

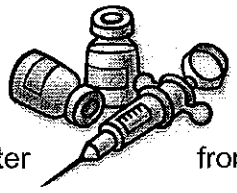
by Professor Gary Warne

This classic text on CAH is available online and has recently been updated. It can be viewed and downloaded at: **http://www.rchmelb.org/cah_book/index.cfm?doc_id=1375**

A must read for all those CAH-affected children (or adults who would have liked this information when they were children at a time when none was available!!)

When your child is facing adrenal crisis, there's *no time* to waste…**You NEED to be ready....**

Keep **SoluCortef** nearby
AND LEARN HOW TO USE IT!



As a back-up, keep a letter from your doctor outlining emergency procedures.

Visit the Adrenal Crisis page on our website for a sample emergency letter:

http://www.caresfoundation.org/adrenalcrisis.html

Rare Disease Legislation Alert

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202-224-3121 and ask for your Senator's office). Remember that mail to Washington is delayed by four or more weeks due to security concerns. If you wish to send a letter, either mail it to your Senator's local state office, or FAX it to the Washington, DC office. As an alternative, you can simply go to: www.senate.gov/senators/senator_by_state.cfmhttp (Select your state) and email your senators.

CAH Consensus Statement

(Continued from page 5)

(NY), Claude Migeon (MD), Walter L. Miller (CA), Jorn Müller (Denmark), Maria I. New (NY), Sharon E. Oberfield (NY), Michael Peter (Germany), E. Martin Ritzén (Sweden), Paul Saenger (NY), Martin O. Savage (UK), Justine M. Schober (PA), Wolfgang G. Sippell (Germany), Janos Solyom (Hungary), Phyllis W. Speiser (NY), Bradford L. Therrell (TX), Judson J. Van Wyk (NC), Garry L. Warne (Australia), Perrin C. White (TX), Ludwig Wildt (Germany), and Selma Witchell (PA). The following also contributed to the material for the article: Peter C. Hindmarsh (UK), Lewis B. Holmes (MA), Lourdes Ibañez (Spain), Lenore S. Levine (NY), Songya Pang (IL), and Anna Wedell (Sweden).

Managing CAH in public schools

(Continued from page 1)

illness and/or at the parent's discretion" and should include a dosage limit, i.e. "up to X mgs".

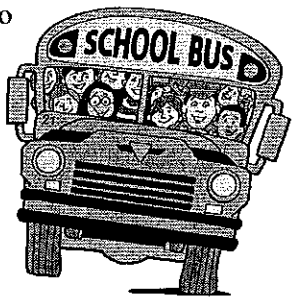
3. ***Meet with your principal.*** Most principals want to be aware of any child at their school who might have unique needs or disorders. This is a good failsafe for an emergency situation if the nurse is unavailable. The principal is in charge of everything that happens at that school; attempting to explain CAH in an emergency to the person in charge results in wasted time.

4. ***Meet with your child's teacher (s).*** This is where your child will be spending his day. Meet with the teachers to give them a brief rundown of what CAH is and why your child might have special needs. Many parents have their CAH child carry a water bottle to prevent dehydration, but be prepared that a doctor's order might be required. Discuss falls on the playground and whether or not you would like to be called for any and all mishaps.

5. ***Try to schedule meds at times that are the least disruptive.*** Fitting in a trip to the nurse's office during a break (perhaps on the way in or out for recess) or in between classes is generally the best way to allow for a school day that is as normal as possible. If there are no breaks in between classes near the needed time, discuss with the teacher the best time to allow your child to leave the classroom.

One issue that might be a difficult one for some of you: ***Discuss with your doctor the Solu-Cortef issue and whether or not s/he considers it a necessity for school.*** While this may seem like an obvious necessity to you, remember that you are dealing with legal issues concerning an IM injection and you may find yourself in a struggle with the school system. Most of us carry the Solu-Cortef kit with us everywhere. However, to require the school to do so can get tricky. Consider field trips, for example. Depending on the rigidity of the school system you are in, many areas will require an RN to be available to give an injection. If this means hiring an RN to accompany your child on all field trips, many school systems will balk. Here's what the American Disabilities Act states: "Public entities are not required to take actions that would result in undue financial and administrative burdens. They are required to make reasonable modifications to policies, practices, and procedures where necessary to avoid discrimination, unless they can demonstrate that doing so would fundamentally alter the nature of the service, program, or activity being provided." (www.ada.gov ADA Title II: State and Local Government Activities). In other words, this is an issue that will vary greatly throughout the municipalities. This is also an area where those in private schools might be told that their child is too great a "risk" to have in their school. Again, carefully consider bringing up the Solu-Cortef issue. If you live or work close to the school, or if you have family or friends versed in IM injections and who can arrive at the school quickly in an emergency, maybe this is an area where you would want to maintain 100% control. Talk to your ped endo about the best course of action for your CAH child.

Many parents choose to leave information with the school nurse concerning CAH. Many parents have a letter written up by their doctor explaining what to do in an emergency, including information and instructions for EMT's, paramedics, or emergency room personnel. There have been varying degrees of success with this approach. CARES Foundation has a few sample letters that have been used. These samples are available on our website under Adrenal Crisis.



We all know that our CAH kids are among the brightest kids out there, and they certainly deserve the best we can give them. Sending them off to a new setting can be scary, but with good communication lines, they, too, can enjoy this "wonderful time of the year"!

Karen Bassler is the mother of an 8-yr-old daughter with CAH as well as a 10-yr-old daughter who is non-CAH. She is a Certified Nurse Assistant who works part-time in the Health Suite of an elementary school in a large metropolitan suburb. Mrs. Bassler was recently appointed a Consumer Seat on the Maryland State Advisory Council on Hereditary and Congenital Disorders.

The Use of Second-Tier Molecular Screening for Improving the Sensitivity and Specificity of CAH Newborn Screening

Edwin Naylor, Ph.D., MPH, President and Laboratory Director of NeoGen Screening, Inc.

A common problem in newborn screening for CAH is that the positive cut-off for 17-hydroxy-progesterone (17-OH-P) is generally set in order to minimize the false positive rate. While this is effective in detecting newborns with salt wasting CAH it misses most cases of non-classical or late onset CAH and some simple virilizing cases. On April 1, 2001, Neo Gen Screening, Inc. received a Small Business Innovation Research grant from the National Institutes of Health to develop second-tier molecular assays for the common CYP21 mutations that cause CAH. These assays will be performed on the original filter paper blood specimen collected in the newborn period whenever there is an elevated 10-OH-P. This will permit us to lower the initial cut-off level while at the same time increasing sensitivity and specificity. It will also permit us to detect significantly more cases of non-classical or simple virilazing CAH than we can using 17-OH-P alone.

In this project we are amplifying the DNA present in the filter paper blood specimen to give us more material to work with and we then use Fluorescence Resonance Energy Transfer (FRET) probes to identify specific CYP21 gene changes. This technology is call "Light Cycler" analysis and is a new and very rapid process that permits us to have our molecular results the same day that we run the newborn screen. We are currently completing the validation of these assays and have begun screening known cases of CAH that we detected at Neo Gen Screening as well as well as cases sent to us from Pittsburgh Children's Hospital, Indiana, and Brazil. These methods will detect the presence of deletions and duplications of the CYP21 gene and will permit us to identify up to 10 of the most common gene changes including the common I2, 8 bp del 706-713, I172N, Q318X, R356W, InsT, P453, P30 and the non-classical V281L mutations. We expect to complete the validation phase by April 1, 2003 and to incorporate it into our routine newborn screening procedures and to offer it to high risk patients on a diagnostic basis.

CAH Study at National Institutes of Health

Bethesda, Maryland

Dr. Deborah Merke

We are currently recruiting children with classic 21-hydroxylase deficiency with a bone age between 2- 13 years (boys) or 2-11 years (girls). Children will be enrolled in the study at the Warren Grant Magnuson Clinical Center of the National Institutes of Health in Bethesda, Maryland.

The conventional treatment of classical congenital adrenal hyperplasia (CAH) involves daily administration of hydrocortisone and fludrocortisone. One of the challenges in treating patients with CAH is finding the best dose of hydrocortisone. Treatment with too low a dose will fail to suppress the androgens optimally; treatment with too high a dose will cause weight gain, slow growth rate, and other features of hydrocortisone excess. This probably explains the finding that (treated) CAH patients average four inches shorter than would be expected based upon their parents' heights. To test the hypothesis that the regimen of flutamide (an antiandrogen), testolactone (an inhibitor of androgen-to -estrogen conversion), and reduced hydrocortisone can normalize the growth and adult stature of children with CAH, and avoid the complications of supraphysiologic glucocorticoid dosage, children with CAH will be randomized to receive either the above regimen or conventional treatment. For more information, contact: *Dr. Deborah Merke or Meg Keil, NP at (301) 435-3391, fax: (301)-402-5618.*

Behavior in Congenital Adrenal Hyperplasia

Sheri A. Berenbaum, Ph.D.
Department of Psychology, Pennsylvania State University

We study behavior in girls and boys with CAH and in their siblings and cousins without CAH in order to understand (1) the relation between early exposure to androgens and various aspects of social behavior and abilities, and (2) any behavioral consequences of the disease itself.

To summarize major findings – Girls with CAH are different from their sisters without CAH in some ways, but not in other ways.

- Girls with CAH have "typical" female gender identity. Most girls with CAH clearly identify themselves as girls and have no wish to be boys.
- It is characteristic of girls with CAH (especially those with salt-wasting CAH) to play with boys' toys in childhood and to continue to be interested in "boy-typical" activities in adolescence (such as sports and electronics). But, girls with CAH are not the same as boys in their activities, there is variation among girls, and there is nothing wrong with girls with CAH who are interested in boys' activities. The results suggest that boy-typical interests result, in part, from effects of androgen that occur during brain development before birth.
- Boys with CAH are generally similar to boys without CAH in their behavior and preferences. For example, there is no difference between boys with and without CAH in their activities, suggesting that differences between girls with and without CAH are not due to general factors associated with having the disease.

We are currently studying several questions following naturally from our previous results.

- Hobbies and occupational interests. Are young women with CAH likely to pursue science and engineering in college, or to continue sports participation?
- Dating and romantic interests. For example, do young women with CAH start dating later than women without CAH? Many girls and parents wonder about this. By continuing this research, we will be in a better position to answer these questions.
- Behavioral effects (if any) of prenatal dexamethasone treatment for girls with CAH and other treated children.
- Behavior in relation to aspects of medical treatment, such as age at surgery.

Our studies involve participants across a range of ages (2 years to young adulthood). **We would be happy to have you join our research program.** If you are interested in participating, please contact us at Psychology, Penn State, University Park PA 16802, 814-863-6018, e-mail: sberenbaum@psu.edu. We travel to visit participants in their homes, so don't hesitate to volunteer even if you don't live in Pennsylvania.

To all our CAH Adults and Families:

We are trying to create a workable database with the full names and addresses of the CAH community. *Please help us to help you.* For many of you we only have a first name and email address. If you haven't already done so, ***please register on our database at***:
http://www.caresfoundation.org/form.html.

Physician Listings Available from CARES

CARES Foundation has compiled a large list of pediatric endocrinologists, some adult endocrinologists, urologists and psychologists with experience in treating CAH/NCCAH patients. Please contact CARES Foundation for more information.

CAH Research at Cornell

Dr. Maria I. New, Weill Medical College of Cornell University

Under the longest running grant issued by the National Institutes of Health, which was recently given a MERIT award (Mechanism to Extend Research in Time), Dr. Maria I. New is pursuing the following investigations related to congenital adrenal hyperplasia (CAH):

1. Prenatal diagnosis and treatment: Dr. New is compiling a complete library of the mutations in the 21-hydroxylase and 11 •-hydroxylase genes which cause classic (severe) and nonclassic (mild, late-onset) CAH. She has the only center in the United States which routinely provides prenatal diagnosis and treatment of classically affected female fetuses. Prenatal treatment with dexamethasone to the mother spares classically affected females genital ambiguity and the need for corrective surgery.
2. Improving final height of children with classic CAH: The combined drug regimen of leuprolide, which suppresses the onset of puberty, plus growth hormone has been shown to be effective in maximizing final height.
3. Fertility in CAH: Dr. New continues to investigate the factors that contribute to infertility in males and females with CAH.
4. Psychobiology of CAH: With her colleague Dr. Heino Meyer-Bahlburg, Dr. New is investigating the role of prenatal androgens in gender identity.
5. Treatment of nonclassic CAH: With one of the largest patient populations of nonclassic CAH in the world, Dr. New continues to refine treatment for the extremely variable symptoms of nonclassic CAH.

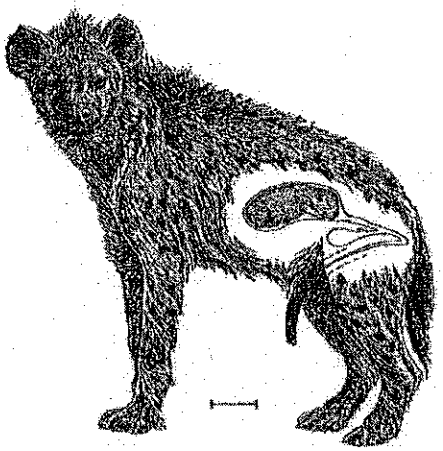
CAH Related Research with Spotted Hyenas

Dr. Ned Place, University of California, Berkeley

Dr. Ned J. Place has been doing fascinating research using spotted hyenas at the University of California in Berkeley. Although spotted hyenas are not perfect animal models for understanding CAH, they do represent an "experiment of nature" in which females are naturally masculinized and exposed to androgens prenatally.

The female spotted hyenas are the most masculinized female mammals ever described. All females of this species have a clitoris that approaches the size and shape of the penis; they also have a pseudoscrotum, as no external vaginal opening exists. Scientists believe females are virilized in response to androgens during fetal development that are derived from the mother's ovary.

Dr. Place is specifically interested in the effects of prenatal androgens on the development of the ovary, and the persistent effects that prenatal androgens can have on ovarian function in adulthood. This has relevance to CAH, as some women with CAH suffer from some degree of PCOS (polycystic ovary syndrome) and associated infertility. Dr. Place is interested in learning how the ovaries of spotted hyenas are affected by prenatal androgens, and if some mechanism might explain how they avoid the negative consequences.



(Illustration by Christine M. Drea, Duke University)

Dr. Place will soon have a paper published in *Biology of Reproduction* with his findings; addressing the possibility that anti-androgen treated female hyenas conceive more readily than their more highly virilized sisters.

Research Summary in Non Classical 21- Hydroxylase Deficiency

Dr. Naomi Weintraub, Institute for Endocrinolgy and Diabetes, Schneider Children's Medical Center of Israel, Petah-Tikva, Israel

We have run several studies over the past few years involving patients with nonclassical CAH (NC21-OHD) at our clinic. In the first study by our team, published in the European Journal of Endocrinology (volume 136: 188-195, 1997), we investigated the relationship of pubertal and bone age (BA) maturation at the start of glucocorticoid therapy with the course of puberty and the final height in subjects with NC21OHD. We found that patients in whom therapy was initiated at least one year before the onset of true puberty and/or bone age of 9 years reached their genetic adult height, whereas those who started therapy during active puberty or at BA more than 9 years, had a final height below their mid-parental height range.

To determine if the clinical variability in NC21OHD is due to genotype differences, our next study was done in collaboration with Dr. Shosh Israel and Dr. Haiim Brautbar from the Tissue Typing Unit of the Hadassah Medical Organization in Jerusalem, who developed the setup for genotyping the CYP21 gene in Israel. The possible association of genotype with ethnic origin was also investigated. The results were published in the European Journal of Endocrinology, (Volume 143, 397-403, 200). Our findings suggest that males with NC21OHD may be under diagnosed. Further, we believe that genotyping is justified in patients with the non-classical form of steroid-21 hydroxylase deficiency owing to the existence of a subgroup (about 30% in our study population) with compound heterozygosity for one mild and one severe mutation. In patients carrying a severe mutation, future genetic and prenatal counseling is advocated as there is a chance of approximately 1:1000-1600 that they will have a daughter affected with classic 21OHD compared to 1:15000 prevalence in the general population and prenatal treatment with dexamethasone for fetuses carrying two severe mutations is now feasible.

In our third study, published in the July/August 2002 issue of *The Journal of Pediatric Endocrinology and Metabolism*, we assessed cortisol response in patients with NC21OHD before and during hydrocortisone therapy, and the findings were related to genotype. We concluded that coverage with a stress dose of hydrocortisone during serious intercurrent illness or surgery should be considered in patients with documented cortisol deficiency.

In conclusion, NC21OHD is a rather frequent entity with a large variability in presentation. A difference in genotype (2 mild mutations vs. one mild and one severe mutation) might explain some of the variance, with the more severe form being associated with earlier chronological age and more advanced bone age at diagnosis, relatively taller stature, and higher frequency of precocious puberty. We do not yet know if the group with more severe disease ends up shorter.

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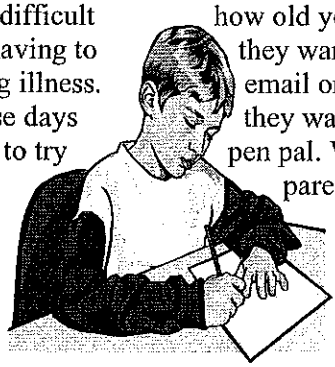
Teen Pen Pals

The teen years are difficult enough without having to cope with having a life-long illness. Teenagers are so adept these days with email that we decided to try to put together a pen pal program for teens. This way, they can connect with other teenagers experiencing some of the same issues. You or your teen can sign up by emailing me at Kelly@caresfoundation.org. Tell me how old your teen is, whether they want to be contacted by email or telephone, whether they want a male or female pen pal. We must also have the parents' permission and must be able to speak to the parents over the phone to obtain this permission. No private information will be released until all parties agree to the arrangement.



We hope that this will help our kids to weather some of the bumps of adolescence knowing that they are not alone.

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CARES SCIENTIFIC and ADVISORY BOARD

Meet our Newest Members...

RICARDO AZZIZ, M.D., M.P.H., M.B.A
Reproductive Endocrinologist

Dr. Azziz is the Chair, Department of Obstetrics and Gynecology, Director of the Division of Reproductive Endocinology and Infertility at Cedars-Sinai Medical Center in Los Angeles. Dr. Azziz has also completed a Masters in Public Health (MPH) and Master in Business Administration (MBA).

Dr. Azziz has published over 200 original articles, book chapters, and reviews. Dr. Azziz's research include the study of the polycystic ovary syndrome (PCOS), the non-classic adrenal hyperplasia (NCAH); the role of the adrenal in hyperandrogenic disorders; the genetics of hyperandrogenic disorders including PCOS and NCAH; the treatment of hirsutism; the regulation and physiology of adrenal androgens; and credentialing and cost-effectiveness of operative endoscopy for pelvic reconstruction.

RICHARD C. RINK, M.D.
Pediatric Urologist

Dr. Richard C. Rink is Chief of Pediatric Urology at the James Whitcomb Riley Hospital for Children at Indiana University.

Dr. Rink is a member of the American Academy of Pediatrics (AAP), American College of Surgeons, The Society of Pediatric Urology, The European Society of Pediatric Urology, and the American Urologic Association (AUA). He has served on the Executive Committees of the Society of Genitourinary Reconstructive Surgeons (GURS), the American Academy of Pediatrics-Section on Urology, and the North Central Section of the AUA. He is past president of both the GURS and American Association of Pediatric Urologists. He is President-elect of the AAP-Section on Urology.

Dr. Rink has authored or co-authored over 120 journal articles and 20 Textbook chapters. He is co-editor of the new textbook, "Pediatric Urology".

His primary interest is in pediatric genital reconstructive procedures and reconstruction of the lower urinary tract in children. He has a tremendous amount of experience in reconstruction for Congenital Adrenal Hyperplasia and has reported several innovative surgical techniques for these children. He has lectured throughout the world on this topic.

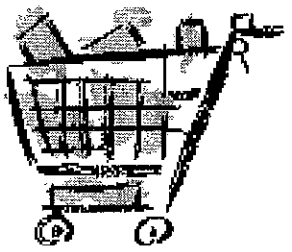
MORE VOLUNTEERS NEEDED!!

We have invitations to host Family Workshops in Northern New Jersey, Los Angeles, Dallas and Indianapolis. We are looking for volunteers in these areas to help coordinate these events. As a volunteer-run organization, we can only provide these conferences with support from you. If you would be willing to help arrange a Workshop in one of these locations or elsewhere, please email Kelly at: kelly@caresfoundation.org or call on the toll-free line. Please consider volunteering.

Attention Kroger Shoppers...

Sandra Billings, a mom with a CAH son in Texas, has developed a method for parents to help fund Dr. Maria New's research.

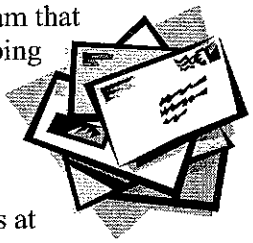
For those of you that live in **TEXAS** or **LOUISIANA**, if you do your grocery shopping at Kroger you could be helping fund CAH Research at the same time. All you have to do is carry a ***Kroger Share Card*** with you and present it to the cashier at check out. The cashier will scan the card and 1% of all purchases in a year will be donated to Dr. Maria New's Gene Therapy Research for finding a cure for CAH. This is an easy way to help fund research without having to take cash out of your pocket (which helps too!). It is basically free money that Kroger gives to CAH Research. If you would like to get a card, *please email Sandra Billings at Billprop1@msn.com or call her at 281-861-6043*. Cards will be mailed out to you. Please give them to friends and family that shop at Kroger as well— every bit helps!



You can use the Kroger share card along with your regular Kroger card and coupons. We need more people to use the cards... So please call or email....

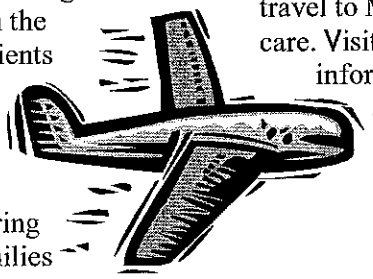
Get Ready...
it's about to go out in the Mail...

CARES is kicking off it's new "Count Your Blessings" Program! With all the stress we face in our daily lives, sometimes we forget the blessings that we *do* have. So, CARES has started a program that will help you count up the blessings in *your* life while helping us carry on the work we do to support our families with CAH. CARES relies on the generosity of individuals, corporations and foundations for its financial support. So, when you receive our package in the mail, please take a moment to count your blessings and be a blessing to others at the same time.



Financial Assistance Available

Often, the most experienced physicians/surgeons are at a great distance from the homes of CAH patients and seeing them requires travel and lodging expenses. CARES Foundation is offering small grants to families who have legitimate financial need to help cover the costs of travel for this purpose. CARES has also negotiated reduced rate rooms at the Helmsley Hotel in New York for families needing to travel to Manhattan for specialist care. Visit our website for more information about travel assistance for medical care.



Meet Meryl....

Meryl Stone (not Streep), our Associate Director, has been working part-time in the CARES office since February. Meryl, in addition to being a wife and mother of two wonderful boys, Benjamin and Matthew, holds an MBA from NYU. In her previous career, Meryl worked as an Information Technology Project Manager on Wall Street before she retired (temporarily) to provide full time care to her family's needs.

While Meryl's family has not been directly affected by CAH, she knows first hand what it means to have a child who requires special attention. Meryl has been an avid advocate for her 9 year old son, Matthew, who has developmental disabilities.

Meryl has spent years working with teachers, administrators, therapists and other parents to provide a more inclusive school environment for children with special needs. Recently, she has developed a website to help other parents better understand the laws and their rights so they can best advocate for their children.

Member of....

CARES is now listed as a member of the following organizations: The Genetic Alliance, a provisional member of National Organization of Rare Diseases (NORD), National Institute of Diabetes Digestive Kidney Diseases (NIDDK) and is also an organizational member of Save Babies Through Screening.

To make your tax deductible contribution to CARES Foundation, please fill out this form and include your check or credit card number. You may also make donations via our website at: http://www.caresfoundation.org

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