

Volume 2  
Issue 1  
Winter 2002

~  
**The  
Research  
Issue -  
Part 2**  
~

**In this Issue**

Monitoring of  
Treatment in  
CAH. . .

Pg 1

Surgery &  
Related Issues. . .

Pg 7

Newborn  
Screening. . . .

Pg 11

Prenatal  
Diagnosis &  
Treatment for  
Classical CAH. .

Pg 15

## **CAH Family Workshop**

Johns Hopkins University Hospital  
Baltimore, Maryland

**Saturday, March 8, 2003**

1:00-6:00 PM

Cost: Free

*Featured Guest Speakers*

**CLAUDE MIGEON**, MD, Pediatric Endocrinologist  
Johns Hopkins Hospital

**DEBORAH MERKE**, MD, National Institutes of Health

**SHERI BERENBAUM**, Ph.D., Professor of Psychology  
at Penn. State University

*Topics:*

- ◇ New Advancements in CAH Treatment and Future Trends
- ◇ General Treatment of CAH/NCCAH
- ◇ Prenatal Therapy
- ◇ Psychological Aspects of CAH
- ◇ Question & Answer
- ◇ Discussion (Networking)
- ◇ Pre-Teen/Teen Group Support Session with Dr. Berenbaum  
(Pre-registration is required)

***Look for your invitation in the mail or visit our website.***

## **CAH Family Support Groups Around the Country**

**ALABAMA**

Contact Susan Davenport  
205-665-1934  
[susand@sepcousa.com](mailto:susand@sepcousa.com)

**ARIZONA**

Contact Michelle May  
480-759-0870  
[michlmay@aol.com](mailto:michlmay@aol.com)

**TEXAS**

Contact Sandra Billings  
281-861-6043  
[billprop1@msn.com](mailto:billprop1@msn.com)

**WISCONSIN**

Contact Lisa Jaskie  
(414) 645-0782  
[lisa1273@msn.com](mailto:lisa1273@msn.com)

## **Monitoring of Treatment in CAH**

*Scott A. Rivkees, M.D.*

*Director, Yale Child Study Center, Pediatric Endocrinology, Yale Department of Pediatrics*

**M**onitoring treatment in congenital adrenal hyperplasia (CAH) is as important as the treatment itself. Yet, monitoring approaches vary from institution-to-institution and from doctor-to-doctor. The recent CAH consensus statement addressed many important aspects related to the care and treatment of CAH. Yet, no specific recommendations were given related to desired hormone levels. Many articles and textbook chapters about CAH also emphasize the importance of monitoring, yet few provide specific details. Not surprisingly, parents and individuals with CAH find it difficult to obtain clear information about acceptable hormone levels and appropriate testing regimens in CAH.

Although it may seem that monitoring and testing in CAH is confusing, there are several approaches that can be used to adequately assess hormone production. It is also very important to emphasize that monitoring changes in physical growth and maturation is as important, if not more

*(Continued on page 3)*

## A Message from the Executive Director:

Dear Friends,

I hope that everyone had a peaceful holiday. I send wishes to all for a happy and **HEALTHY** 2003! This past few months has been very exciting here at CARES Foundation, Inc. We have started in earnest our fundraising campaigns and are having some success. I deeply thank those of you who were able to support us with a tax-deductible contribution and hope that others can help in this effort as well. We need your financial help to continue and expand our service to the CAH community.

We have had some terrific victories in the newborn screening arena, with Ohio mandating the addition of CAH newborn screening and New York (finally) beginning CAH screening in October. Many CARES families wrote letters and made phone calls, and your actions made the difference. Our voices are being heard! This winter, we need to turn our energies to other states that are looking at expansion, to make sure that these states implement comprehensive newborn screening that includes CAH! Please read the *Newborn Screening Update* article on page 11 for full details.

Since our last newsletter, I have had the opportunity to represent the CAH community in a couple of capacities. I am now a member of the Newborn Screening Diagnosis and Follow-up Workgroup, Maternal and Child Health Bureau of The Health Resources and Services Administration, United States Department of Health and Human Services. The purpose of this Workgroup is to develop uniform

guidelines for all the states in the US for follow-up and diagnosis. In this capacity, I can ensure that the needs of CAH babies and parents are well considered in the national guidelines.

In November, I met with the intramural research staff and extramural research officer at the National Institute of Child Health and Human Development at NIH to discuss ways to increase research related to CAH/NCCAH. I found them all so encouraging and supportive of our efforts. We are quite fortunate to have intramural researcher, Dr. Deborah Merke at NICHD because she has chosen to focus much of her research on CAH. I am quite optimistic that this was the beginning of a nice relationship between the CAH community and NIH. I expect to go down to NIH in Bethesda, MD again this winter to discuss research to benefit women of reproductive age with CAH/NCCAH. I will keep you posted on the results of that meeting as well.

I also attended a meeting hosted by NORD (National Organization of Rare Diseases) in New York City. The purpose of the 2-day meeting was to bring the leaders of rare diseases support groups together with the personnel from the Office Of Rare Diseases and other Institutes at The National Institutes of Health. I learned so much about the "System" and what we need to do as a rare disease community to increase research focused on CAH. I also had the opportunity to meet the leaders of many other rare disease organizations. It was terrific

meeting so many dedicated people working to help those affected by rare diseases. We had so much in common.

Be Well all and again, Happy New Year!

Warm Regards,

*Kelly*

### FOUNDERS

Kelly and Adam Leight

### BOARD OF TRUSTEES

Kelly Rosso Leight, President  
K. Adam Leight, Vice President  
Vivian Altman Quintanilla, Treasurer  
Janet A. Wolkoff, Esq., Secretary  
Abigail Krueger Bialer  
Elizabeth Demaree  
Nancy Kislin Flaum  
Risa Perlmutter Goldstein  
Pamela Knight Kretsge  
Sarah Macyshyn  
Michelle May, MD  
Roberta Preston  
Hope Z. Raphaelian  
Deborah Green Taffet

### SCIENTIFIC & MEDICAL

#### ADVISORY BOARD

Ricardo Azziz, M.D.  
Susan W. Baker, Ph. D.  
Sheri A. Berenbaum, Ph.D.  
Daniel Gunther, M.D.  
Maria I. New, M.D.  
Dix P. Poppas, M.D.  
Richard Rink, M.D.  
Phyllis W. Speiser, M.D.  
Bradford L. Therrell, Ph.D.

## **Monitoring of Treatment in CAH**

*(Continued from page 1)*

important, as the laboratory testing in CAH.

### **Monitoring growth and maturation in CAH.**

#### ***Growth and Weight:***

The rate of growth provides very important clues about treatment in CAH. In general, with proper treatment the child with CAH should grow along the same percentile for height, which reflects the height of the parents.

Between two years of age and puberty, the average child grows about 2-1/2 inches per year and gains 2-3 pounds for every inch of height gain. During infancy and puberty rates of growth are even faster than during childhood. In general, a child will usually grow along the same percentile on growth charts from infancy through adolescence. Thus, height and weight need to be both monitored and plotted on standard growth charts to assess growth in CAH.

Looking at growth charts and following changes in height and weight, one can detect signs of over- and undertreatment. If glucocorticoid (hydrocortisone, prednisone, dexamethasone) doses are too high, growth will slow and weight will increase. It takes about 3-6 months to appreciate changes in growth rates (changes in height). Changes in weight, though, can be seen much

sooner. Increases in weight, above and beyond that which is normally expected (more than 3 lbs per inch of growth; more than 7 lbs per year), can be a sign of overtreatment. Thus, it is very useful for families to monitor weight at home. For example, if the weight increases by more than one pound over 2-4 weeks after a dose change, it may be a sign that the dose is too high.

Whereas slowing of growth can represent signs of overtreatment, increased growth can reflect undertreatment. With undertreatment, there is increased androgen production, which can stimulate growth. Undertreated children may therefore climb to higher height percentiles on growth charts.

#### ***The Importance of Regular Follow-up:***

To assess physical changes in CAH and be able to respond to signs of over- or undertreatment in a timely manner, many practitioners will see individuals with CAH every 3-4 months. Because signs of over-treatment (facial roundness) can be subtle, it is preferable to see the same practitioner at each visit.

There are physical signs that clinicians can see that suggest either over- or undertreatment. With overtreatment, the face can become round. With significant overtreatment, striae (purple "stretch-marks") can occur. Features of undertreatment include dark or "dirty"-looking knuckles caused by

excessive ACTH secretion. Stomach pain and being excessively tired are also symptoms of undertreatment.

The blood pressure can provide clues about mineralocorticoid (Florinef, fludrocortisone) treatment. If the blood pressure is elevated, this may indicate that the mineralocorticoid dose or salt supplementation is too high and should be reduced. Yet, if the dose is normal or too low, the blood pressure is normal.

Signs of pubertal development are also monitored. In girls, one of the earliest signs of puberty is breast development. In boys, enlargement of the size of the testes is the earliest signs that puberty has started. If puberty begins less than seven years of age in girls and less than nine years of age in boys, it is said to be early or "precocious". Because the adrenal hormones can affect the pituitary gland, precocious puberty is seen in CAH and warrants attention.

#### ***The Usefulness of Bone Ages:***

One of the best tools for monitoring changes in physical maturation is the "bone age". The growth centers, which can be easily visualized with an x-ray of the hand, provide a wonderful marker of long-term androgen secretion. As children get older, the shape of the growth centers changes and have a characteristic appearance at each age. By comparing the size and shapes of

*(Continued on page 4)*

#### **Disclaimer:**

Any communication from CARES Foundation, Inc. is intended for informational and educational purposes only and in no way should be taken to be the provision or practice of medical, nursing or professional health-care advice or services. The information should not be considered complete or exhaustive and should not be used in place of the visit, call, consultation or advice of your physician or other health-care provider. You should not use the information in this or any CARES Foundation, Inc. communication to diagnose or treat CAH or any other disorder without first consulting with your physician or healthcare provider. The articles presented in this newsletter are for informational purposes only and do not necessarily reflect the views of CARES Foundation, Inc.

**Kelly R. Leight**  
**Executive Director**  
Kelly@caresfoundation.org

**Meryl I. Stone**  
**Associate Director**  
Meryl@caresfoundation.org

*This newsletter is published 3 times a year.*

## **Monitoring of Treatment in CAH**

*(Continued from page 3)*

the growth centers in the child's hand to those found in a book of standards, a "bone age" can be determined. Because there is variability from practitioner to practitioner in bone age interpretation, it is useful to have bone ages interpreted by the same individual. Also, some pediatric endocrinologists may be more experienced in interpreting bone ages than general radiologists.

When there is excessive androgen secretion, the skeleton matures at a more rapid pace than usual. This will result in an advanced bone age. Thus, an undertreated child at 6 years of age may have a bone age of 9 years of age. Yet, if the bone age is within a year or so of the actual age, this suggests that treatment has been fine.

The bone age also reflects hormone secretion over the preceding 6-12 months. Changes in the bone age may lag behind recent periods of excess androgen secretion. Many practitioners therefore obtain bone ages every 6 to 12 months.

## **Monitoring of Hormone Levels in CAH**

The levels of adrenal hormones in the blood vary over the 24-hour day. Cortisol and androgen production is highest in the morning and lowest in the afternoon and evening. Hormone levels are also affected by medications. Following a dose of glucocorticoids, androgen levels will fall. Yet, as the medication wears off, hormone levels may rise excessively. Care must be taken to consider the time of day and the timing of doses when interpreting hormone levels.

There are several different approaches that can be used to assess adrenal hormone production. Urine

testing is a "gold standard" and can be used to measure hormone production through out the day. Blood testing provides important information about hormone production and is preferred by many clinicians to due to convenience. Testing of hormone levels several times a day using filter paper specimens has also been shown to be an effective monitoring tool, but is not widely available.

### ***Urine Testing:***

A single blood test measures androgen levels at one time of day. In comparison, a 24-hour urine collection reflects androgen secretion over the 24-hour day and is therefore recognized as the "gold standard" in assessing hormone production.

To assess adrenal hormone and androgen production one measures 17 ketosteroids (17KS) and pregnanetriol in the urine. The 17 KS are breakdown products (metabolic products) of androstenedione and testosterone. Pregnanetriol is the breakdown product of 17-hydroxyprogesterone (17 OHP). To assess 17-hydroxyprogesterone (17 OHP) production, one measures levels of pregnanetriol, which is a metabolite of 17 OHP.

Creatinine is also measured in urine samples. Creatinine is a breakdown product of muscle and is continuously released into the urine. It is produced at a rate of about 10-15 mg/kg (4-6 mg/lb) per day. Measuring the amount of creatinine in the sample indicates if the 24-hour collection is complete or incomplete.

Urine collections are saved in containers provided by hospital or commercial laboratories. They can be conveniently collected on a

weekend day and avoid or reduce the need for blood-sticks. Collections are performed by having the child urinate into the toilet on the morning that the collection starts. The urine is then collected over the entire day, and the urine from the first void the following morning is also collected. The container is kept in a cool place until it is brought to the laboratory.

The elimination of 17 KS and pregnanetriol in the urine increases with age. The values obtained in a 24-hour collection can be compared to normal rates of excretion. 17 KS levels provide the best marker of androgen production. Even in situations in which there is adequate treatment, pregnanetriol levels can be elevated. Thus, when 17 KS and pregnanetriol levels do not agree, more emphasis should be placed on the 17 KS value.

### ***Blood Testing:***

Assessing control from a single blood test is very commonly used due to its convenience. However, a single test may not always reflect if there is adequate control of adrenal gland activity. One also needs to consider the time of day and the timing of doses in interpreting blood levels. Some hormone levels are also better than others in assessing treatment.

A number of hormones that reflect adrenal gland activity can be measured in the blood. These factors include ACTH, 17 hydroxyprogesterone (17 OHP), androstenedione, and testosterone. Electrolytes and renin are be used to assess mineralocorticoid replacement.

Of these different hormones, androstenedione and testosterone most closely match 24-hour 17 KS production and reflect adrenal androgen production. These hormones are especially useful in

*(Continued on page 5)*



**Monitoring of Treatment in CAH**  
(Continued from page 4)

prepubertal children and females. Because testosterone levels rise in puberty in males, testosterone levels are not as useful in adolescent or adult males. In comparison with androstenedione and testosterone, 17 OHP levels can fluctuate widely and may be elevated even when there is good control. The pituitary hormone ACTH has been shown to provide a nice measure of control and is elevated 75% of the time when there is undertreatment.

For children without CAH and not in puberty, average levels of androstenedione are 25 ng/dl, average levels of testosterone levels are 5 ng/dl, and average 17OHP levels are 50 ng/dl. During puberty, levels of these hormones rise. It is possible to achieve normal levels of these hormones in children with CAH. Yet, treating CAH to "normalize" all hormone levels, especially 17 OHP levels, can result in growth suppression and weight gain. Thus, many clinicians aim for androstenedione and testosterone levels that are normal or modestly (about 25%) above normal. Because 17 OHP levels can fluctuate widely and be elevated when there is adequate treatment, some clinicians will accept mid-day 17 OHP levels of 500-1000 ng/dl; others will aim for lower levels.

Morning levels of 17 OHP, androstenedione, and testosterone are much higher than mid-day levels, especially when there is undertreatment. This occurrence reflects the general observation that adrenal glands becoming more active in the early morning hours and at a time when the medication from the day before is wearing off. It can therefore be very useful to obtain

morning hormone levels.

It has been recently shown that when there is good control of adrenal gland activity, 17 OHP levels are less than less than 600 ng/dl in the morning before medication is given and less than 200 ng/dl during the day. In undertreated individuals, 17 OHP levels average 10,000 ng/dl in the morning before the dose, and 5000 ng/dl during the day.

To measure if the child is getting enough salt and/or fludrocortisone, renin and electrolyte levels are measured. An elevated renin levels indicates a need for more salt and/or fludrocortisone. A suppressed renin suggests that the dose of salt and/or fludrocortisone is too high.

**Filter Paper Specimens:**

Whereas a single blood test during the day can provide important insights into CAH control, they can sometimes be misleading. If a sample is obtained in an undertreated child a few hours after a dose of hydrocortisone has been given, levels of 17OHP can decrease. As the medication wears off, 17 OHP levels can increase dramatically.

One can overcome potential pitfalls of obtaining once daily samples by obtaining filter-paper specimens over the course of the day. Children with diabetes check their blood sugar by finger stick 3-4 times a day to be able to properly dose insulin levels. Similarly, one can measure 17 OHP levels on filter paper specimens taken at different times of day. Thus, one can identify times of day when levels are high and others when levels are low and adjust doses accordingly. Filter paper 17OHP levels can be

measured by state-laboratories that perform newborn screening for CAH using filter-paper specimens.

**Conclusions**

The proper monitoring the child with CAH is essential for optimizing treatment and ensuring normal development. Following height and weight is extremely important in the monitoring process, and frequent follow-up is recommended. Bone ages are useful, as they reflect long-term androgen secretion. The measurement of 17 KS in the urine, or androstenedione or testosterone in the blood provide nice measures of adrenal androgen production. Although published specific recommendation for the acceptable hormone levels in CAH are few, many clinicians will aim for levels of androstenedione, testosterone and 17 KS that are normal or modestly (about 25%) above normal. Because blood 17 OHP levels can vary widely in CAH, higher than normal 17 OHP levels are acceptable, but are usually less than 1000 ng/dl with adequate treatment. Because there are different ways to assess if treatment is effective, it is important that you know and understand your physician's approach in monitoring CAH.

**Normal Hormone Levels (not CAH):**

Average number is given in bold. The normal range of levels is in (parentheses).

<b>Hormone</b>	<b>Prepubertal</b>	<b>Mid-Pubertal and adult</b>
<b>Blood testing</b>		
ACTH (pg/ml)		<b>30</b>

(Continued on page 6)

### Monitoring of Treatment in CAH

(Continued from page 5)

(10-60)	<b>30</b> (10-60)	<b>30</b> (10-60)		
Androstenedione (ng/dl)	<b>25</b> (8-50)	<b>70</b> (50-100)	<b>115</b> (70-200)	
17 OHP (ng/dl)	<b>40</b> (3-100)	<b>80</b> (10-150)	<b>100</b> (25-250)	
Testosterone (ng/dl)	<b>5</b> (3-10)	Males: <b>150</b> (100-300)	<b>600</b> (300-1000)	
		Female: <b>25</b> (15-35)	<b>30</b> (10-55)	
<b>Urine testing</b>				
17 Ketosteroids (mg/24 hr)	<b>1.5</b> (0.2- 3)	Males <b>5</b> (3-10)	<b>15</b> (10-25)	
		Female <b>3.5</b> (2.5-8)	<b>10</b> (6-14)	
Pregnanetriol (mg/24 hr)	<b>0.5</b>	<b>1.0</b>	<b>2.0</b>	

-In CAH, levels of androstenedione, testosterone and 17 ketosteroids that are normal or modestly (about 25%) above normal are acceptable. Because blood 17 OHP levels can vary widely in CAH, higher 17 OHP levels are acceptable, but are usually less than 1000 ng/dl with adequate treatment.

-To convert ng/dl units to pmol/L, multiply androstenedione levels by 34, 17 OHP by 30, testosterone by 34.

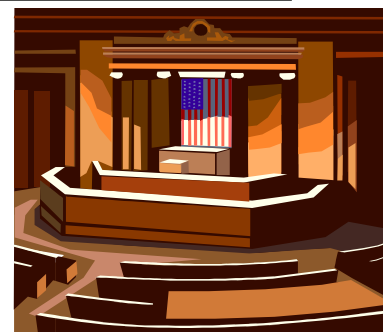
### Selected References<sup>1-7</sup>

1. Appan S., Hindmarsh P. C., and Brook C. G. (1989) Monitoring treatment in congenital adrenal hyperplasia. *Arch Dis Child.* 64, 1235-1239.
2. Bode H. H., Rivkees S. A., Cowley D. M., Pardy K., and Johnson S. (1999) Home monitoring of 17 hydroxyprogesterone levels in congenital adrenal hyperplasia with filter paper blood samples. *J Pediatr.* 134, 185-189.
3. Charmandari E., Matthews D. R., Johnston A., Brook C. G., and Hindmarsh P. C. (2001) Serum cortisol and 17-hydroxyprogesterone interrelation in classic 21-hydroxylase deficiency: is current replacement therapy satisfactory? *J Clin Endocrinol Metab.* 86, 4679-4685.
4. Clayton P. E., Miller W. L., Oberfield S. E., Ritzen E. M., Sippell W. G., and Speiser P. W. (2002) Consensus statement on 21-hydroxylase deficiency from the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society. *J Clin Endocrinol Metab.* 87, 4048-4053.
5. Esoterix (2002) Endocrinology expected values. [http://www.esoterix.com/endocrinology/related/expected\\_values.pdf](http://www.esoterix.com/endocrinology/related/expected_values.pdf).
6. Lee P. A., Urban M. D., Gutai J. P., and Migeon C. J. (1980) Plasma progesterone, 17-hydroxyprogesterone, androstenedione and testosterone in prepubertal, pubertal and adult subjects with congenital virilizing adrenal hyperplasia as indicators of adrenal suppression. *Horm Res.* 13, 347-357.
7. Migeon C. J. and Wisniewski A. B. (2001) Congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. Growth, development, and therapeutic considerations. *Endocrinol Metab Clin North Am.* 30, 193-206.

## H.R. 4013 & H.R. 4014 Have Been Passed by Congress!!

On October 17, 2002, both H.R. 4013 (the Rare Disease Act) and H.R. 4014 (the Rare Disease Orphan Product Development Act) were approved by the Senate, after having earlier been approved by the House of Representatives. The Bills were signed by President Bush on November 2, 2002 and became law. CARES is grateful to all who joined us in support of these important Bills, which will greatly increase rare-disease research supported by the National Institutes of Health (NIH) and the U.S. Food & Drug Administration (FDA).

CF



# Virilized Girls with CAH: Surgery Considerations

*Kelly Leight, Executive Director, CARES Foundation*

*Dan Gunther, M.D., M.A., Assistant Professor of Pediatrics, University of Washington*

*Susan Baker, Ph.D., Psychoendocrinologist, Weill Medical School of Cornell University*

**S**o, you have just been told that your baby girl has a genetic disorder called Classical Congenital Adrenal Hyperplasia. You are scared, confused and upset. Aside from the medical aspects of the disease—adrenal crisis, the need for medication and careful medical monitoring for the rest of her life, you are now confronted with the decision of what to do with her genitals. They don't look like your conception of what a normal female should look like. Should your daughter undergo reconstructive surgery? Below are a few key points to consider.

## **OUR PHILOSOPHY:**

CARES Foundation, Inc. is here to support all CAH families and affected individuals. In the past most virilized girls with CAH underwent surgery—often called “feminizing genitoplasty”—due to a long held belief in the importance of “normal” looking genitalia for healthy social and sexual development. Recently, the importance and desirability of correcting the genitalia has been questioned by some. Though many families still opt for surgical correction in infancy, some have now chosen to wait until the child is older and can be involved in the decision-making process. Still others will not consider surgery at all for their daughters. This is a personal decision to be made by the family, in consultation with their physicians, based on the medical situation specific to each child. CARES Foundation does not endorse any specific course of action, but is here to support all families under all circumstances.

## **IS SURGERY THE RIGHT DECISION? --INFORMED CONSENT:**

Parents need to be informed about all their options regarding surgery. Is the surgery really “necessary”? The difference between a surgical procedure that is medically necessary and one that is purely cosmetic is an important consideration, and one that is not always black or white. For instance, some parents might consider the construction of a vagina in a female to be “necessary”, whereas reducing the size of the clitoris may be seen as merely “cosmetic”—therefore they may opt for the former procedure but not the latter. Some may see neither procedure as being necessary, at least not before menstruation (why do you need a vagina as a child?), while others might fear that the social or psychological consequences of “being different” are so great that surgical correction is truly “medically necessary”. Others might argue that a procedure need not be “necessary” in the strictest sense to be beneficial and desirable.

Most would agree that conditions that threaten health need to be repaired—such as a blockage or other anomaly that causes urine to reflux (back up) into the bladder or the kidneys that can lead to infection.

There are no right or wrong answers for every case. Each case and every family is different. Only you can decide what will work for best for your daughter and your

family. You will be tempted to ask the doctors “what would you do?” But, ultimately, you need to make the decision. Unfortunately, there are few studies that look at long-term follow-up of CAH reconstructive surgery, and no studies that compare the well being of those that have had surgery to those who haven't.

Be sure to weigh carefully all facts, testimonies and resources that are available to you before arriving at a decision. Remember that once you have opted for a surgical procedure, it will not be reversible.

## **THE PEDIATRIC UROLOGIST/SURGEON:**

CARES Foundation, Inc. also believes that the skill and experience of the pediatric urologist/surgeon is of foremost importance. The 2002 CAH Consensus Statement from Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology states that surgery “should only be performed in centers with significant experience”, and further defines this as “a center with experience of at least 3-4 cases/year”. This often means that you may have difficulty finding a surgeon with the requisite experience in your state, since there are only a few centers in the US that meet these criteria. The surgeon should be willing to let you know exactly how many genital reconstruction surgeries he/she performs each year. If the answer seems vague to you, i.e. “I've done several” or “a few”, press for a more specific answer to your question. Don't be afraid to ask for “before and after” pictures. The response to your

*(Continued on page 8)*

## Virilized Girls with CAH: Surgery Considerations

(Continued from page 7)

inquires should give you a pretty good idea of whether you wish to put your daughter in the hands of that particular surgeon. Remember, a good physician will never resent you seeking a second opinion.

CARES Foundation, Inc. can provide you with a list of pediatric urological surgeons who are experienced with these types of surgeries. This is not to suggest that they are the only qualified surgeons. It is important that you select a surgeon that you and your daughter will be happy with—you're likely to have a relationship for many years to come.

### PSYCHOLOGICAL SUPPORT:

CARES Foundation, Inc. believes that your decision should not be made without support. As parents, there is a great deal of pressure to make the right decision for your daughter and to understand all aspects of the surgery as best you can. If your daughter is under the care of a pediatric endocrinologist at a major medical center, you may have already been directed to a psychologist, social worker or therapist experienced in helping parents deal with serious illness. Psychologists specialize just as physicians do, so it is important to find a psychologist who is trained to identify and meet your child's special needs. Pediatric psychologists focus on the development of children who have medical conditions, and their families. Unfortunately, not all institutions have psychologists or other counselors skilled in dealing with CAH and related disorders. Just as in the case of surgeons, CARES Foundation, Inc. can help you to

identify a qualified mental health professional. We believe that only the parents, in consultation with the endocrinologist and surgeon, and with the support of an experienced psychologist, can decide what is



"Nurse, get on the internet, go to **SURGERY.COM**, scroll down and click on the 'Are you totally lost?' icon."

best for their daughter given the extent of virilization and medical issues of each individual child.

Developing a long-term relationship with a mental health professional will also be beneficial to your child as she grows. You can expect that she will have many questions about her body and her disease. A good mental health professional can help you to answer questions thoughtfully and can counsel your child when she needs support.

In addition, CARES Foundation can connect you with other parents with CAH girls who can lend support, listen and share their experiences.

### SEX ASSIGNMENT:

A sex assignment of female is recommended for the vast majority of CAH virilized 46, XX infants. This preserves the child's fertility and is in line with the child's chromosomes. The issue of sex assignment only really arises with the Prader 5 infant (extremely virilized—completely resembles

male genitalia). Some have suggested that these infants should be raised as males. However, there have been very few children born in the US where this choice has been made and no published studies reviewing these

few cases. The issue was raised because some investigators speculated that Prader 5 infants would have greater brain effects of testosterone, mirroring the effect on their genitalia, and therefore be prone to gender dysphoria. However, the few reports that exist on CAH women who elect to change their sex assignment as adults indicate that they come from Prader 3,4 and 5, not just Prader 5, and that

in general, gender dysphoria is quite rare in CAH in all Prader categories. As a result, the 2002 CAH Consensus Statement states that, "there is insufficient evidence to support rearing a 46, XX infant at Prader stage 5 as male".

This is a different situation from a child who is mis-identified at birth as male and raised as a male for some significant period of time, then determined in later childhood to be 46, XX with CAH. The Consensus statement recommends that

"[c]onsideration for sex reassignment must be undertaken only after thorough psychological evaluation of patient and family. Surgery appropriate to gender assignment should be undertaken after a period of endocrine treatment". In these cases, the patient may remain in a male gender assignment and may consider surgery and pharmaceutical treatment to accomplish this. This may include removal of the ovaries, testicular implants and hormone therapy.

(Continued on page 9)



## **Virilized Girls with CAH: Surgery Considerations**

*(Continued from page 8)*

Mastectomy may be desired as well. Some patients, under these circumstances, do choose a female sex assignment and may consider genitoplasty surgery.

### **TIMING OF SURGICAL PROCEDURES:**

Some adult women with CAH have urged parents to defer the decision on non-life threatening reconstructive surgery until the child is mature enough to participate in the decision making process. Others are glad that they did not have the burden of making that decision. There is little guidance here and parents must make a decision that works for their family.

If early surgery is chosen, The 2002 CAH Consensus Statement states, “[b]ased on recent clinical experience, the recommended time for surgery is at 2-6 months, although this is not universal practice. It is important to note that surgery is technically easier than at later stages.” However, with that said, it is most important that you, as parents, have had the time to gather all of the information about surgery and have full informed consent. Early surgery is only rarely necessary, so you must feel comfortable with this decision.

### **CLITORAL REDUCTION AND VAGINOPLASTY:**

Clitoral reduction surgery and vaginoplasty are two separate procedures, but are often done at the same time when early surgery is chosen. Clitoral reduction surgery involves reducing the size of the clitoris by removing a portion of the erectile tissue. If done properly, the nerve bundles are preserved and carefully placed intact. The CAH Consensus Statement states that, “[s]

urgery to reduce clitoral size requires careful consideration. Total removal of the clitoris should never be performed. If clitoral reduction is elected, it is crucial to preserve the neurovascular bundle, the glans, and the preputial skin related to the glans.... The early operation should be a one-stage complete repair using the newest techniques of vaginoplasty, clitoral and labial surgery...”

Vaginoplasty involves rebuilding the vaginal area to improve functioning of the vagina and urethra. Adult women with CAH caution that any surgery to the genital area will reduce sexual sensitivity. The CAH consensus statement says, “We acknowledge that there are concerns about early surgery. However, surgical techniques have improved. We urge caution in judging outcome from outdated procedures. Systematic studies are needed to evaluate ultimate function for all girls undergoing surgery.” The adult women with CAH, note that it is difficult to obtain functioning data due to the fact that this surgery is done in infancy and functioning cannot be evaluated well until the child becomes sexually active.

### **SUMMARY:**

The lack of reliable data makes this decision all the more difficult for the parents. Each child is different and each family has different values and thoughts about this process. As parents, we do our best under the circumstances and given the resources available to us at the time. This is all that you can do. So, make sure that you have done your homework, obtained support, thought about it long and hard, and if surgery is elected, see the best, most experienced surgeon

you have access to.

## **OTHER RELATED CONSIDERATIONS**

### **PROTECTING YOUR CHILD’S MODESTY AND PRIVACY:**

As parents, you must be sensitive to your child’s privacy and modesty--especially as she grows older. Most major institutions with experienced specialists in CAH will also be “teaching” hospitals. In such an environment your doctor may feel it’s appropriate (even an obligation) to allow doctors in training—medical students, residents, fellows—to learn from her condition. Physicians do have to be trained, and remember, this is how the doctor that takes care of your daughter learned. Unfortunately, what is best for training physicians is not always best for patients—especially children. Adults with CAH often speak of the shame of being “put on display” as part of the teaching process. Though not an issue with infants, for older children this can be embarrassing, confusing, and stressful. Once you establish a relationship with a physician--probably a pediatric endocrinologist--insist that he/she be the one who follows your child routinely, and that genital exams be done only by them if possible. A fellow (specialist in training) may become part of the team, but ask that it be the same fellow at each visit and someone who is expected to be involved for several years. Open discussion with your child about her condition and the need and reason for doctor visits may help to reduce anxiety.

Your doctor may wish to take photos of your child. This could be an appropriate alternative to a parade of doctors needing to “see for

*(Continued on page 10)*

## **Virilized Girls with CAH: Surgery Considerations**

*(Continued from page 9)*

themselves". They also allow for progressive follow-up, teaching, and education of the families seeking answers. It is best if the physician take the pictures, and only after an explanation of how the pictures may be used, and sensitive reassurance given as to privacy and confidentiality. Older children should give their own consent.

### **SECRECY AND SHAME:**

When adult women with CAH look back at their childhood experience, many of them report that their most painful memories revolve around a sense of secrecy and shame. Some of these women did not even know they had undergone genital surgery until they were well into adulthood. In the past, parents were often encouraged by their doctors not to discuss genital differences or surgery, to discourage questions by the child, and to keep the situation secret from extended family members. This practice stemmed from an unproven belief that focusing on genital differences might lead to ambivalence on the part of the child (or even parent)—and might eventually result in an unstable gender identity.

Though perhaps well intentioned at the time, the policy was ultimately damaging—in some cases disastrous. Secrecy did not eliminate conflict or anxiety in the child—it fanned it. Children have radar for lies and deception. Silence is interpreted as shame. In the absence of light, children will invent scenarios far worse than the truth.

CARES Foundation strongly encourages families and physicians to be open and honest about all aspects of your child's condition and medical

care. Most physicians now accept that dishonesty with their patients—even children—is never ethically acceptable. Your child's questions should be answered in an age appropriate manner (see below). If you don't know the answer, simply tell them that—and find someone who does. Though not always easy, honesty truly is the best policy.

### **HOW DO I TALK TO MY CHILD ABOUT HER CONDITION AND SURGERY?**

#### **ANSWER**

**by Susan Baker, Ph.D.:**

What to tell an affected child, and at what age is a very complex question. The answer largely depends on the child's sex, age, and the family situation, so has to be discussed and decided on a case-by-case basis. For example, some children are very curious and ask a lot about their medical condition, why they have to go to the doctor, get tests and so on when their siblings don't. Such questions should always be fully and honestly answered in age appropriate ways.

A special case with respect to information is that of young girls who have had genital surgery. Most young girls won't have the background information to ask or wonder about the early surgery, (unless they had a poor genitoplasty) to ask, for example, why they look different in their genital area than their sisters. In such cases it is usually best to wait until the child's own questions and resulting increasing knowledge about their medical condition lead up naturally to their learning about the early surgery. If information is given at the right pace this usually occurs at or near the teen years, a time when most girls have learned discretion, and when many may

need to be fully informed so as to partake in the decision whether to have or defer vaginoplasty if it wasn't done in infancy. (If the child doesn't ask, one can egg her [or him on non surgical issues] on to start doing so with questions like, "How come you never asked why you have to see the doctor every so many months?" and so on.)

For a young teen to understand having had the surgery (and maybe the need for a vaginoplasty, which they will need to think and make decisions about), they need to have a pretty good basic understanding of CAH. I usually do this with our patients starting at age 5 to 7, seeing the child every year or so, again varying with the child's temperament and family. I meet with the child alone, then finish by asking the child if she would be willing for us to meet with her parents and for her to tell them what we talked about, with me to help if she gets stuck. That way everyone walks away knowing what was discussed, and able to discuss it at home. It also gives me a check on whether the child had a misunderstanding of anything we talked about. Telling too young children who don't have such a background about surgery can be scary for them, and leave them feeling frightened and confused. Also telling them before they have a sense of the consequences if they talk about what they have learned to other children without using discretion can cause another set of problems.

It is most important for parents to be open to informing their children as the children grow. Parents with a classical CAH affected child, particularly parents of an affected daughter with a genital birth defect often feel traumatized long after the

*(Continued on page 11)*

## Virilized Girls with CAH: Surgery Considerations

(Continued from page 10)

birth and sex determination.

Sometimes this leads them to not want to tell their children anything, feeling that their children will feel the same trauma. When this happens to the parents, the parents unwittingly pass on to the child the sense that there IS something wrong, but it is something too awful and scary to ask or talk about. These children later grow up to feel, among other things, that there is a failure of trust between them and their parents, and that they were lied to by parents and doctors alike.

What to tell and when is very individual, as I said at the start. The only absolute rule I have that doesn't depend on the specifics of the family is that you must never lie or evade with a child. It is okay to say, "I'm not sure of the answer to that, let me

call the doctor and find out?" even if you just need to buy a little time to think over your response to a tricky question. But you must get back and answer the question, in an age appropriate way. If the child never asks questions, parents have to ask themselves if they have been sending subtle messages to the child that she (this occurs more often with girls for the reasons mentioned above) had better not ask any questions about what she has, why she goes to the doctor, why she has blood tests frequently, why she has to take medication, and so on. If this occurs it is a signal that it is time to get experienced professional help.

CF

*I would like to thank the following people for their help with this article: Dr. Sheri Berenbaum, Dr. David Sandberg, Dr. Scott Rivkees, Dr. Dix Poppas, Dr. Rick*

*Rink, Dr. Garry Warne, parents—Michelle, Adina and Kaye, and the stories of CAH adult women.*

---

## Newborn Screening in the States: Update

Ohio leads the news here with the decision to mandate CAH newborn screening, beginning in April 2003! At the meeting where the decision was made, the chair of the committee read and distributed the letters written by our CARES Foundation families. Those letters moved the committee to do the right thing. Way to go Ohio families!!! New York finally began its CAH newborn screening in October after many delays. We are so pleased that they finally got the program up and running and began saving CAH babies.

While we will continue our efforts to encourage California, Utah, Oklahoma and Vermont to add CAH newborn screening, we can add

Nevada and Nebraska to the list.



The contracts for newborn screening services are up for renewal this year for both of these states. This means it is a prime time to begin urging those states to add CAH newborn screening. Please consider writing letters to urge these states to add CAH screening, especially if you are a resident (but all letters help whether you live in the state or not). If you can't write, please call them.

**Nebraska (Contact both):**  
*Mr. Ron Ross, Director*

Nebraska Department of Health and Human Services  
P.O. Box 95044  
Lincoln, NE 68509-5044  
Asst. Rachel Rezabek, email: [rachel.rezabek@hhss.state.ne.us](mailto:rachel.rezabek@hhss.state.ne.us).  
Phone number: (402) 471-9106

*Richard Raymond, M.D.*  
Chief Medical Officer, NHHS  
P.O. Box 95007  
Lincoln, NE 68509-5007  
Asst. Roxie Anderson, email: [roxie.anderson@hhss.state.ne.us](mailto:roxie.anderson@hhss.state.ne.us)  
Phone Number: (402) 471-8566

And to email Governor Mike Johanns, <http://gov.nol.org/Johanns/mail/govmail.htm>

(Continued on page 12)

# Changing the Birth Certificate or Birth Record

*DaleLynn Sims*

The birth record or birth certificate. A small little piece of paper and information that forever identifies an individual by the data contained therein, filled with mundane information on the parents, date, time and where the blessed event occurred. For the most part it is locked away in a closet or safety deposit box only to appear for an occasional need such as beginning school a passport or the like. With the majority the story ends here. Some however find one bit of information on the record cause for concern--that is the designation under 'SEX'. In states without newborn screening for CAH, a female child with CAH may be sent home with "male" written on their birth certificate.

While inconsistent from state to state, most states allow for the correction or amending of the birth record. Some states issue a new record changing all the data except the date of issue; some states will not change records. Indiana does not include 'sex' on their birth record and some states will amend rather than

issue new records. Some amended records like those from Florida will reflect only that the record is amended with no evidence of what was corrected. Others like Mississippi require a court order

and will issue an amended birth certificate with the gender typed in the margin, but the old gender remaining unchanged.

Most states rely on medical records dating back to birth

and or affidavit from the attending birth physician. This can be simple as was recently done in Ohio where the parents of a CAH female infant obtained her daughter's new birth certificate by submitting a statement from the attending physician indicating a mistake had been made.

For adults seeking to change the records because they were not changed during childhood by the parents, it can sometimes take years to acquire the old medical records; some are sealed, some take court

orders to release and some are just no longer available. Without these, one must rely on the documentation provided by current medical caregivers, submitting these to and working with the respective state Department of Health to request the record change. With all the documents submitted, the new birth certificate received will have the correct designator in the 'SEX' box.

Here we have outlined the basic information regarding birth records. The states have come a long way, however it has taken years and we must continue to promote the advancement and diffusion of knowledge and understanding on these issues to ensure that those that follow us benefit from our work.

For contact information on your State Registrars and the Department Of Health please see: <http://www.kindredspirittlakeside.homestead.com/birthrecord.html>

CF

## **Newborn Screening Update**

*(Continued from page 11)*

### **Nevada:**

*Yvonne Sylva, Administrator,*  
Nevada State Health Division  
505 East King Street Room 201  
Carson City, NV 89701  
email: [ysylva@nvhd.state.nv.us](mailto:ysylva@nvhd.state.nv.us)  
Phone number: 775.684.4200

And to email Governor Kenny Guinn: <http://gov.state.nv.us/mailgov.htm>

In *California*, Dr. George Cunningham, the Director of the

State Genetics Program, has been requesting permission to begin CAH newborn screening for a couple of years now, but Governor Gray Davis keeps denying his request based on the funding needed. Please write to Governor Gray Davis and let him know that his refusal to approve the Genetics program request to add CAH newborn screening is leading to death and/or significant trauma for our children. At least 45 children with Classical CAH are born each year in California. Please write and

ask him to save CAH babies born in California! You can't put a price tag on these babies' lives!

### **California:**

*Governor Gray Davis*  
State Capitol Building  
Sacramento, CA 95814  
Phone: 916-445-2841  
Fax: 916-445-4633  
Email: [governor@governor.ca.gov](mailto:governor@governor.ca.gov)

In *Utah*, the state is still considering adding diseases to their newborn

*(Continued on page 16)*



# Psychological Development in CAH

*Heino F.L. Meyer-Bahlburg, Dr. rer. nat.*

*Program of Developmental Psychoendocrinology, Department of Psychiatry, Columbia University*

**O**ur Research Program has a long track record of psychological research in children, adolescence, and adults with either inborn hormonal disorders or a history of prenatal hormone treatment. We are interested in finding ways of improving the quality of life for people living with any of these conditions, and also hope to gain a better understanding of the effects of hormones on psychological development in general. Several studies are currently underway on children and adults with CAH.

## **1. Psychological outcome after prenatal dexamethasone treatment**

Increasingly, dexamethasone (DEX) is prescribed for the treatment of pregnant women who are likely to give birth to a girl with CAH. DEX is given to replace the cortisol, which the CAH fetus does not produce, and to thereby reduce the production of excess androgen. Dr. Maria New and others had already shown that successful DEX treatment will indeed reduce or eliminate the effect of excess androgens on genital development, which then reduces or eliminates the need for genital surgery later. We are now conducting two broad-band studies, in collaboration with Dr. Maria New at Weill Medical College of Cornell University in New York City, to see whether DEX-treated children with CAH differ in cognitive development, temperament, and general adjustment from DEX-unexposed children with CAH and from non-CAH control children. In the first study, mothers of approximately 500 children, ages 3 months to 12 years, completed a battery of age-

appropriate questionnaires about their children. In the second study, 140 children, ages 5-12 years, underwent psychological tests, interviews, and behavior observations, and their mothers were also interviewed. Data collection in both studies is completed, and data analysis and peer review of the results is currently in progress.

## **2. Children with CAH compared to children without CAH**

The two studies above will not only give us information about the effects of prenatal DEX, if any, but also information on behavioral differences between children with CAH and controls. In addition, we are currently collaborating with Dr. Catherine Hall and her colleagues in Manchester, U.K., in a psychological study contrasting girls with CAH to girls with diabetes mellitus, in order to separate the effects of a chronic hormonal condition and the associated medical care from those that are specific to CAH. Data from this study are also currently being analyzed.

## **3. Adult women with CAH**

While we have already learned quite a bit about the psychological outcome of children with CAH, especially girls, we know much less about what adult life with CAH looks like. Thus, again in collaboration with Dr. Maria New, we have embarked on a long-term follow-up study on adult women with CAH. Here, we are interested in long-term development in terms of education and occupation, partnerships, marriage, child-bearing/rearing, and

general adjustment. In addition, we want to find answers for a number of specific questions. 1. How do the more severe forms of classical (prenatal-onset) CAH differ from the milder forms in psychological outcome? 2. How does the psychological outcome of classical (prenatal-onset) CAH differ from that of non-classical (postnatal-onset) CAH? 3. Does the specific molecular configuration of the 21-hydroxylase gene abnormality help us to predict psychological outcome? 4. How does the genital status at birth and subsequent genital surgery affect the quality of romantic/sexual life? We are nearing the end of data collection and data analysis has begun. We are also collaborating with Dr. Miroslav Domic (Zagreb, Croatia) in a similar, but smaller study of CAH women in Croatia.

Once the complex data analysis of these various studies is completed and the findings have undergone critical peer review, we will summarize them for the CARES Foundation.

CF

## **Physician Listings Available from CARES**

**C**ARES 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.

# Improving Newborn Screening for CAH

## Using Tandem Mass Spectrometry

Dietrich Matern, MD, and Piero Rinaldo, MD, PhD  
*Biochemical Genetics Laboratory, Mayo Clinic, Rochester, MN*  
<http://www.mayo.edu/bgl/>

Following the development of an immunoassay to determine the concentration of 17-hydroxy progesterone (17-OHP) in blood spots in 1977, newborn screening for CAH was introduced into several newborn screening programs

worldwide. However, in the USA babies are currently screened for this disorder in only 34 states. The reason for this limited penetrance is not a disagreement about CAH being an important disorder that should be identified and treated as early in life as possible, but the fact that the

immunoassays available are associated with a high number of false positive results. In other words too many babies not affected with CAH have an abnormal screening test. This is particularly true for premature neonates because their blood often contains compounds that the available screening tests cannot differentiate from 17-OHP. However, every abnormal result has significant consequences because they must be followed up to ensure that no affected baby is mistakenly left behind. This requires collecting additional blood specimens to measure 17-OHP and other steroids. Minimizing the number of these false positive results is important because there would be fewer families experiencing the emotional stress of an abnormal screening result and of the inevitable

consequences (consultation with endocrinologist, laboratory testing, unnecessary care).

To achieve the goal of improving newborn screening for CAH, we have developed an assay using tandem mass spectrometry (MS/MS). This technology has gained a prominent position among analytical methods due to its versatility, unmatched sensitivity, and specificity. Since the 1990s, MS/MS is becoming an integral part of newborn screening programs because of its ability to detect more than 30

disorders in a single blood spot and a single analysis. CAH is not one of these disorders, but it is possible to specifically detect 17-OHP utilizing this technology. Furthermore, using MS/MS one is not limited to a single analyte but other steroids can be identified simultaneously. As indicated in the figure, CAH deficiency not only causes the elevation of 17-OHP and other steroids (i.e., androstenedione), but also results in relatively low cortisol concentrations. Using this multi-analyte approach, the specificity of newborn screening for CAH can be improved significantly.

In a retrospective study we determined 17-OHP, androstenedione, and cortisol in more than 700 blood spots that had previously been tested by

immunoassay. Using MS/MS 95% of the initially labeled false positives were eliminated. The analytical time required for this MS/MS method is currently not compatible with its use as a primary screening test of hundreds of samples per day. However, it can still significantly reduce the false positive rate of the conventional immunoassays as a second tier test which means that newborn blood spots that yield elevated 17-OHP concentrations are re-analyzed using MS/MS to determine the final screening result.

This approach can also be taken by molecular genetic testing for the most common mutations in the CAH gene (CYP21) as described by Dr. Naylor in the previous CARES newsletter (CARES Foundation 2002;1(3):10). However, genetic testing has limitations because patients carrying less common mutations would remain unidentified. Biochemical testing using MS/MS on the other hand is typically abnormal in a patient with CAH independent of the frequency or type of the gene defect involved.

The MS/MS assay described here is currently being validated and is anticipated to become available by the spring of 2003.

-----  
Figure: Pathway of steroid synthesis.

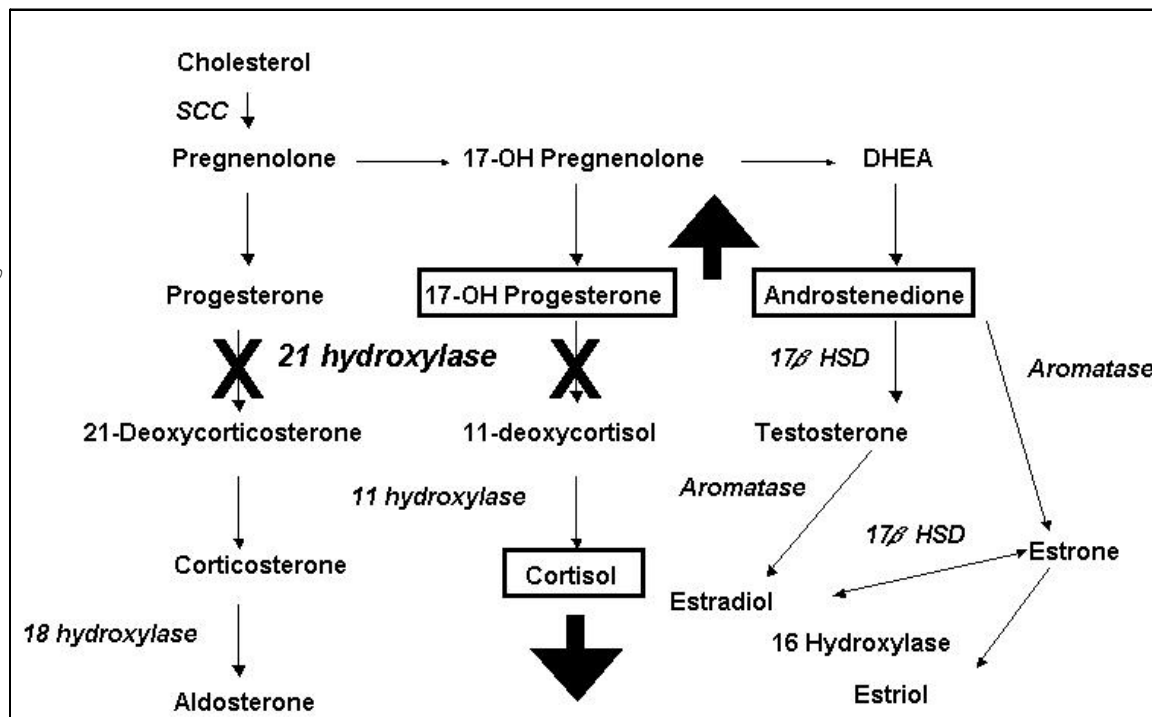
(Continued on page 15)



## Improving Newborn Screening for CAH Using Tandem Mass Spectrometry

(Continued from page 14)

21-Hydroxylase deficiency accounts for approximately 95% of disorders affecting this pathway and causes classic Congenital Adrenal Hyperplasia (CAH).



## \*Prenatal Diagnosis & Treatment for Classical CAH

Elizabeth Kitzinger, Weill Medical School of Cornell University

**\*NOTE:** Since time of publication in 2003, CARES has published additional articles on this controversial subject. Please read our [2007](#) & [2009](#) articles for a more in-depth discussion of the pros and cons of Dexamethasone prenatal treatment.

While newborn screening for CAH is very much in the news these days, few people are aware that prenatal diagnosis and treatment are also available. Prenatal treatment of CAH is uniquely important for affected girls, because treatment of the mother with low-dose dexamethasone, which crosses the placental barrier, prevents the formation of ambiguous (male-like) genitalia in the developing female fetus. This makes corrective surgery unnecessary and permits definitive sex assignment at birth, because the external genitalia are correctly matched with the perfectly normal internal sex organs of CAH-affected girls.

Prenatal treatment has been used

since 1984. In the United States, the only center routinely offering prenatal diagnosis and treatment is Dr. Maria New's clinic at New York Presbyterian Hospital-Weill Medical Center (Cornell) in New York City. Dr. New has treated over 600 pregnant women at risk for the birth of a CAH-affected child. Treatment begins as soon as pregnancy is confirmed. Chorionic villus sampling at 9-11 weeks' gestation permits sex karyotyping, and treatment is discontinued if the child is male. DNA analysis of the fetus permits diagnosis of the child as affected (classical or nonclassical forms of CAH can be distinguished) or unaffected. Classically affected females are then treated to term. The results are remarkable.

Dr. New maintains contact with all children treated prenatally, and has found no adverse developmental consequences. Thus, with nearly 20 years' experience, the treatment appears to be safe for

mother and child, though there are endocrinologists who are wary of using dexamethasone prenatally even now.

It is important to note that prenatal diagnosis and treatment should **ONLY** be done in a clinic like Dr. New's with long experience and commitment to follow-up. Only by tracking the growth of prenatally treated children can the long-term effects of treatment be exhaustively studied. Administering dexamethasone to achieve normal genitalia requires the judgment and experience of specialists. The benefits to families of classically affected girls cannot be underestimated. We hope that the availability of this treatment will be shared with all families at risk for the birth of CAH-affected



CF

# Hydrocortisone Infusion Pump Study

Sheila Gunn, M.D.

Assistant Professor of Pediatrics, Baylor College of Medicine

**C**ongenital Adrenal Hyperplasia (CAH) is caused by a metabolic defect in the production of cortisol and aldosterone in the adrenal gland. Adrenocorticotropin hormone (ACTH) is released by the pituitary gland and stimulates the adrenal gland to produce cortisol. Most of the release of ACTH occurs during the night in pulses that rise in the early morning between 4-6 am. In the child with CAH, cortisol is not produced causing a feedback rise in the amount of ACTH. There is also a rise in other hormones including 17-hydroxyprogesterone (17-OHP) and the male hormone androstenedione. Management of CAH requires the administration of hydrocortisone (cortisol) and fludrocortisone several times daily in amounts that will suppress the 17-OHP, androstenedione and ACTH to normal levels. One of the problems is that the amount of hydrocortisone that is needed to suppress the hormone levels may cause poor growth and weight gain.

The purpose of this study is to determine if administration of hydrocortisone by an infusion pump during the night will suppress ACTH, 17-OHP and androstenedione levels so that a lower dose of hydrocortisone can be used. In this study, a group of girls with CAH age 9-15 and a group of normal girls age 9-15 will have two studies to determine their hormone levels. Each girl will have a screening history, physical exam and test for

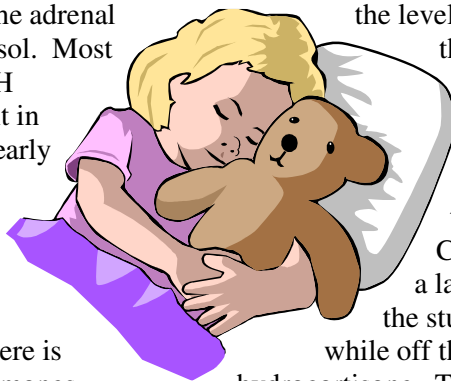
anemia. In the first study, the girls will be admitted to the GCRC and have an IV placed using a numbing medication and they will continue to take their home medication. They will have blood drawn several times through the IV to determine the levels and pulses of the ACTH, 17-OHP and androstenedione for 24 hr. In the second study, the girls with CAH will return at a later date to have the study repeated while off their

hydrocortisone. They will receive several pulses of hydrocortisone through an infusion pump during the night. The hormone levels will be analyzed to determine if the infusions of hydrocortisone suppressed the ACTH levels and lowered the 17-OHP and androstenedione levels.

Interested persons can call the endocrine research nurse Sue McGirk, R.N at 832-822-3063 or e-mail at [tsmcgirk@TexasChildrensHospital.org](mailto:tsmcgirk@TexasChildrensHospital.org).

*Sheila Gunn is the principle investigator for this study. She is an assistant professor of pediatrics at Baylor College of Medicine in the Pediatric Endocrine Section. This research is being done at Texas Children's Hospital at the General Clinical Research Center (GCRC).*

CF



## Newborn Screening Update

(Continued from page 12)

screening program, but CAH is NOT under strong consideration right now. We need to change that!

### Utah:

V. Fan Tait, M.D.

Director of CSHCN

Utah Department of Health

44 North Medical Drive

Salt Lake City, Utah 84113

(801) 584-8239

(801) 584-8488 (fax)

Asst. Adrienne Alward email:

[aalward@utah.gov](mailto:aalward@utah.gov)

Email Dr. Tait: [ftait@utah.gov](mailto:ftait@utah.gov)

And to email Governor Mike Leavitt: [governor@utah.gov](mailto:governor@utah.gov).

CF

## Did You Know...

**K**elly Leight sits as a member of the Newborn Screening Diagnosis and Follow-up Workgroup under the Maternal and Child Health Bureau of The Health Resources and Services Administration for the US Department of Health and Human Services. She is a member of the Public Affairs Committee of the March of Dimes-New Jersey. She is also the New Jersey representative for Save Babies Through Screening, an organization that advocates for comprehensive newborn screening for life-threatening genetic disorders. She has been appointed by former New Jersey Governor Donald DiFrancesco to serve as a Commissioner on the New Jersey Catastrophic Illness in Children Relief Fund Commission. She was also appointed in 2002 by Governor James McGreevey to the New Jersey Advisory Commission on the Status of Women.

CF



# Non-Classical CAH in Adult Women of Reproductive Age

Ricardo Azziz, M.D.

Chair, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, California

**N**on-classic (a.k.a. delayed or late onset) adrenal hyperplasia (NCAH) due to 21-hydroxylase deficiency affects between 2% and 10% of hyperandrogenic women, depending on ethnicity. Dr. Ricardo Azziz, currently Chair of the Department of Obstetrics & Gynecology at Cedars-Sinai Medical Center, has been studying the epidemiology, physiology, and genetics of the disorder for the past 15 years. Some of the highlights of Dr. Azziz's research include:

1) Determining the prevalence of NCAH in unselected hyperandrogenic women in the Northeast (at the Johns Hopkins Hospital) and Southeast (at the University of Alabama at Birmingham) United States, and Puerto Rico (at the University of Puerto Rico). These studies indicated that the prevalence of NCAH in hyperandrogenic women in the United States is approximately 2%, although it may be lower in the African-American population.

2) Using prospective studies, the technique of screening for the disorder among hyperandrogenic women with the use of a basal 17-hydroxyprogesterone measurement, was studied. Essentially, a cut-off value of approximately 2 ng/ml for a basal 17-HP level obtained in the follicular phase of the menstrual cycle has a positive predictive value for NCAH of 16%; hormone levels below this cut-off value essentially exclude affected patients.

3) The early genetics of the disorder of NCAH were studied, and a unique mutation (PRO-453 to Ser) was first reported.

4) The risk of clinically-evident hyperandrogenism in carriers

(heterozygotes) for congenital 21-hydroxylase deficiency was also assessed and was found to be relatively minimal.

5) The mechanisms underlying the excess androgen production in NCAH, in spite of relatively normal circulating ACTH levels, were studied and indicated that the androgen excess was primarily due to intrinsic defects in enzyme kinetics and to associated ovarian hyperandrogenism.

6) The clinical presentation of NCAH was studied in a large multi-center study and it was found that, contrary to earlier reports, the hyperandrogenic symptoms of the disorder appear to be progressive over time.

7) Other studies also indicted that there appears to be a loose association between the severity of the phenotype (appearance of the disorder) and the severity of the genotype (type of genetic abnormality).

Dr. Azziz has also coordinated a large multi-center collaborative group for the study of NCAH. The NCAH multi-center international study group includes investigators from the following sites:

- The University of Alabama at Birmingham, Birmingham, AL, USA.
- Instituto Mexicano del Seguro Social, Mexico City, Mexico.
- The University of Palermo, Palermo, Italy.
- Centre Hospitalier et Universitaire de Lille, Lille, France.
- University of Pisa, Pisa, Italy.
- Hospital Sant Joan de Deu, Barcelona, Spain.
- Hospital das Clinicas, Sao Paulo, Brazil.

- Hospital de l'Antiquaille, Lyon, France.
- Centre Hospitalier Universitaire D'Angers, Angers, France.
- North Shore University Hospital, Manhasset, NY, USA.
- Faculty of Medicine of Porto, Porto, Portugal.
- Hospital Ramon y Cajal, Madrid, Spain.
- University of Pittsburgh, Pittsburgh, PA, USA.

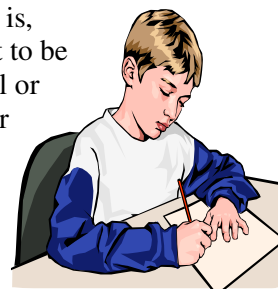
CF

## Teen Pen Pals

**T**he 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](mailto: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.

CF



## 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 offers 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.

CF

## Have your Supermarket Contribute to CARES

Attention all Texas members. Thanks to Ann Davis, CARES Foundation is now a charity member of the *Good Neighbor Program* in **Tom Thumb, Randalls and Simon David** supermarkets.

The next time you're at one of these supermarkets, remember to pick up a Reward Card application at the courtesy booth to fill out and link your card to our account. The supermarket will pay us a percentage of our account total, so be sure to use your card every time you shop. By using your card, you

will also be eligible for exclusive discounts, giveaways, enter-to-wins, direct mail rewards and Airmiles.

CF



## Pharmaceutical Patient Assistance Programs

The organization called PhRMA has a list of patient assistance programs offered by each drug company for prescription drugs at <http://www.phrma.org/pap/>. If you cannot pay for medication, these programs can help.

On that same internet page in the right hand column, it has links for other types of government supported and private assistance programs.

CF

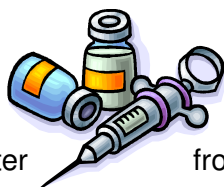
## More Volunteers Needed!!

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](mailto:kelly@caresfoundation.org) or call on the toll-free line. Please consider volunteering.

CF

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  
emergency procedures.

from your doctor outlining

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

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

## 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>.

CF

[illegible]

```
ERROR: undefined
OFFENDING COMMAND: pp_clip

STACK:
```