

# CDH NEWS

The MassGeneral Hospital *for* Children & Children's Hospital Boston  
Congenital Diaphragmatic Hernia Study Newsletter

## Research Update

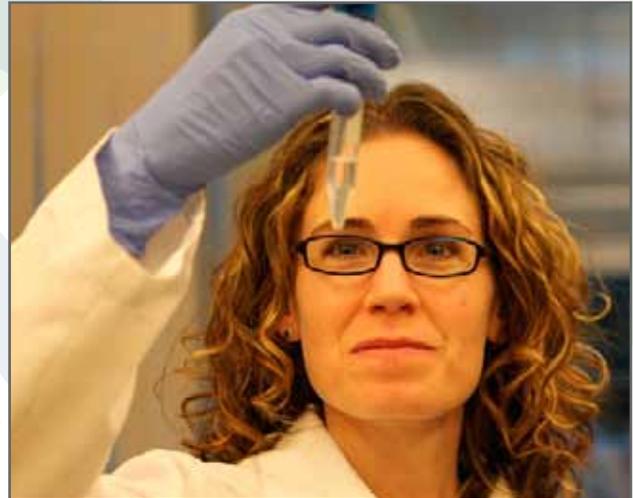
From Dr. Meaghan Russell

During the last several years, the Donahoe laboratory and collaborators have been working together on a project that combines findings from several different genetic methods. Collectively, these data can be used to better identify and understand genes involved in normal diaphragm development and CDH.

As previously described in the "Genetics 101" section of Newsletter-Issue 1 (February 2006), living organisms are composed of cells that contain DNA (deoxyribonucleic acid). DNA is a molecule that holds important genetic instructions the body needs to develop and function. These instructions are called genes and each person has 25,000 to 30,000 of them; together, genes make up our genetic blueprint. Unfortunately, very little information is known about the portion of the genetic blueprint that is responsible for diaphragm development.

The diaphragm is thought to form between the 4th and 12th weeks of pregnancy. At the very beginning of diaphragm formation, several tissues in the embryo come together to give rise to a sheet-like structure. This thin fibrous structure does not yet contain any muscle. In many, but not all patients, CDH is believed to result from

*Continued on page 3*



Dr. Meaghan Russell in the laboratory.

## Want to Share Your Family's Story?

Our patient's stories are a vital component of our newsletters. They are particularly helpful to newly diagnosed families. If you have a CDH story you would like to share with our families, please contact us for more details. We would love to publish it in our next newsletter!

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**Helpful Resources P.2**  
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**Kid's Corner P.12**

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## CDH Resources

The Association of Congenital Diaphragmatic Research, Advocacy and Support (CHERUBS) (a support group for families of children with CDH):  
<http://www.cherubs-cdh.org>

CHERUBS Australia: <http://au.geocities.com/ozcherubs/>

CHERUBS United Kingdom: <http://www.uk-cherubs.org.uk/>

Yahoo Listserv for CDH Families:  
<http://health.groups.yahoo.com/group/Breathof-Hope/>

SHARE Pregnancy and Infant Loss Support, Inc. (early pregnancy loss, stillbirth, or infant death support):  
<http://www.nationalshareoffice.com/>

The Compassionate Friends (non-profit organization providing resources and support for grief resolution):  
<http://www.compassionatefriends.com/>

MUMS National Parent to Parent Network:  
<http://www.netnet.net/mums>

The International Birth Defects Information Systems website:  
<http://ibis-birthdefects.org/start/diaphern.htm>

### How to Reach Us:

**Children's Hospital Boston**  
300 Longwood Avenue,  
Fegan 3  
Boston, MA 02115  
617-355-2555  
[CDHResearchStudy@tch.harvard.edu](mailto:CDHResearchStudy@tch.harvard.edu)

**MassGeneral Hospital for Children**  
Charles River Plaza  
185 Cambridge Street, 6-214  
Boston, MA 02114  
617-726-0828  
[mrussell@partners.org](mailto:mrussell@partners.org)

## GIVING FOR A CAUSE: CDH FUNDRAISER



Dr. Patricia Donahoe receiving a \$2,500 donation from Alison Pfeister

Alison and Kent Pfeister, owners of TLC Child Development Center in Hudson, Ohio, became interested in supporting CDH research efforts after they learned of CDH through their daughter, Meaghan Russell. Dr. Russell has worked for a decade on the genetics of diaphragm development and CDH in the Pediatric Surgical Research Laboratories (PSRL) under the guidance of Dr. Patricia Donahoe. Meaghan recently received her PhD degree for this work. On May 21, 2010, TLC Child Development Center sponsored a fundraiser for CDH research. All proceeds and donations from the TLC Art Show and Silent Auction went to the PSRL at the MassGeneral Hospital for Children. The \$2,500 donation provided financial support for summer students in the laboratory. ■

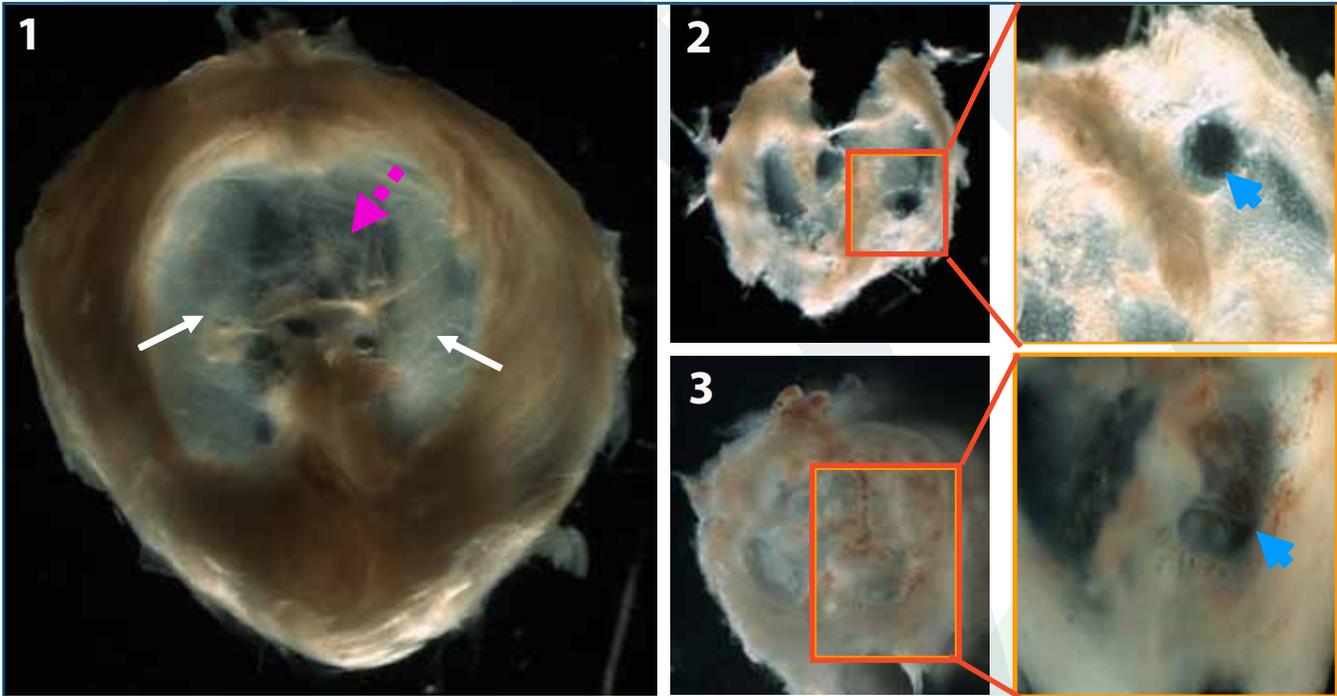
## DID YOU KNOW?



Pediatric Surgical Research Laboratories is now on Facebook! Become a friend & "like" our CDH page.

genetic defects during this initial stage of diaphragm development (only ~4 to 5 weeks into the pregnancy). Since it is difficult, if not impossible, to collect embryonic diaphragm tissues during the first trimester of pregnancy, the genetic instructions that guide the initial events of diaphragm formation are extremely difficult to study in humans. For this reason, we work with mice, a common and well-studied laboratory animal.

(Russell et al., 2012). Using this approach we were able to predict and identify a new CDH-associated gene, called Pbx1. Further studies are required to learn about the specific role of this gene in diaphragm formation and whether mutations in PBX1 are associated with human CDH.



(1) Normal mouse diaphragm. White arrows indicate muscularized regions, and purple dotted arrow indicates central tendon region.

(2 & 3) Blue arrows indicate diaphragm abnormalities in mice with a mutation in the Pbx1 gene. Orange boxes indicate areas of magnification shown on the right.

In our study, we learned about the genes that control events of early and late diaphragm development by analyzing which genes are “on” or “off” during the formation of the diaphragm. Technically, we measured gene expression levels in mouse diaphragm tissue specimens. Instead of studying gene expression on a gene-by-gene basis, as others have done, we analyzed almost every gene in a single experiment. This is called a transcriptome analysis. Our findings were published in The Proceedings of the National Academy of Sciences (PNAS) entitled, “Novel Congenital Diaphragmatic Hernia Candidate Genes Derived from Embryonic Transcriptomes”

This summer we are adding a new genetic approach to our study. We will begin to look for mutations in the DNA of several hundred patients in our CDH study cohort. We will not only analyze the DNA that makes up the PBX1 gene, but also the DNA of many other genes identified through our research and that of others. Our biologists and computer scientists plan to use these data to obtain what we hope will be a more complete picture of the genetic basis of congenital diaphragmatic hernia. ■

## LUNG PROBLEMS IN CHILDREN WITH CDH

By Anna Frangulov, B.S., Barbara Pober, M.D.,  
& Virginia Kharasch, M.D.

The lungs, one of our essential body organs, are often not functioning properly in a child born with CDH. Complications arising from this problem are a main concern to doctors and parents who provide care for children with CDH. In this article we will discuss some of the common lung complications and available interventions for children born with CDH.

### How do lungs normally work?

The most important function of the lungs is to exchange gases, that is, bring oxygen into the body and remove carbon dioxide (CO<sub>2</sub>) and other gases your body does not need. As a person breathes in, the ribcage expands and the diaphragm moves down allowing

the lungs to bring air in. The *diaphragm* is the large muscle and tendon that separates the lungs from the organs in the abdomen (such as the intestines, stomach, and liver). As a person breathes out, the ribcage and diaphragm relax.

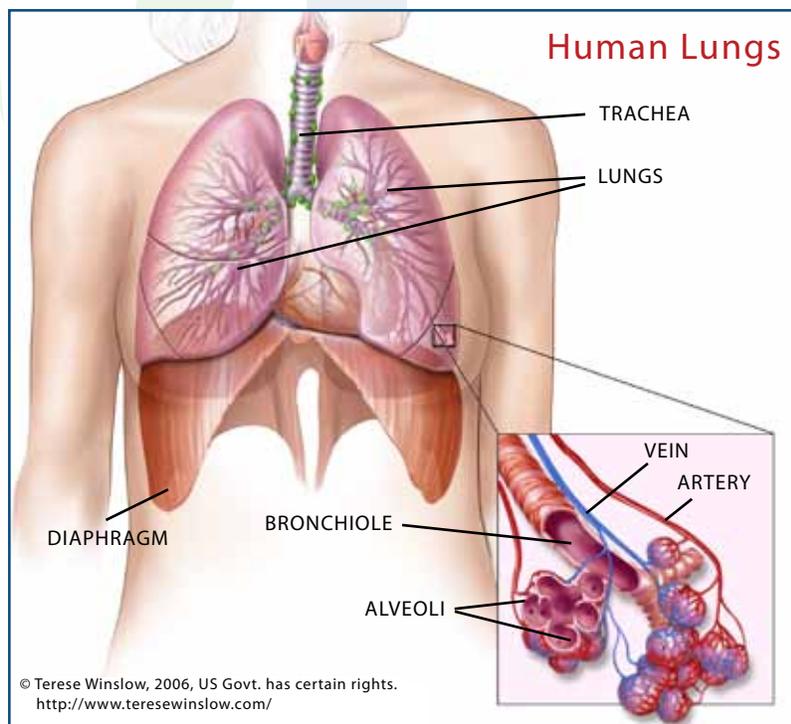
When a person breathes in, the air passes through the nose and mouth, enters the voice box (*larynx*) and windpipe (*trachea*). The trachea splits into two left and right breathing tubes (called *bronchi*) which, in turn, divide into tree-like branches that get narrower and narrower (called *bronchioles*). At the end of the smallest bronchioles are tiny balloon-shaped air-sacs (called *alveoli*); these are surrounded by hundreds of blood vessels that enable oxygen to be carried into the blood stream and carbon dioxide and waste gases to be exhaled out (see diagram).

### When do lungs normally develop?

Lungs begin to form during the 4th week of pregnancy. The windpipe and voice box develop first. Over the next several weeks, the bronchi form a series of branches. As the bronchial branching becomes more extensive, alveoli develop, and more blood vessels continue to form. By the 26th week of pregnancy, the basic process of lung development is complete. In other words, the baby has all the necessary components for breathing and could even survive if he/she is born pre-term. However, alveoli continue to increase in number after birth until the child reaches 8 years.

### How are lungs different in a child with CDH?

At birth, practically all children with CDH have lungs that are smaller and not quite fully mature. Researchers used to think that these problems stemmed from the fact that the abdominal



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<http://www.teresewinslow.com/>

organs (e.g., liver, intestines, liver, and/or stomach) were pushed into the chest during development, due to the CDH. This shift would then compress the lungs and prevent them from properly forming. Current research, however, indicates that this is only the first part of the problem. The lungs of a child born with CDH are not only physically smaller than normal, but the lungs' components differ as well. Lungs in a baby with CDH typically have fewer airway branches, blood vessels, and alveoli, as well as smaller bronchi and bronchioles - appearing as if development was never fully completed. This process is observed in both lungs even if the CDH is only on one side. It is now believed that, in at least some children with CDH, the lungs' problems are due to a combination of factors, a so-called "1-2 punch". The 1st punch is that both lungs are not normally formed from early on in pregnancy, maybe due to lack of stimulatory hormones, while the 2nd punch is compression of the lungs on one side due to the diaphragm defect that occurs later in pregnancy.

## What are different types of lung problems?

How well the lungs develop and function strongly correlate with outcomes for a baby with CDH. The two most common lung complications in children with CDH are:

### ***Pulmonary Hypoplasia***

Pulmonary hypoplasia is a condition where the lungs have an abnormally low number of alveoli and the lungs' artery walls are thicker than normal. This prevents the lungs from performing proper gas exchange and affects how well the child can breathe. Today, pulmonary hypoplasia poses the greatest threat to survival of a baby with CDH. Although the cause is still poorly understood, some of the contributing factors are thought to be genetic, airway pressure, and programmed cell death (apoptosis).

### ***Pulmonary Hypertension***

Pulmonary hypertension is a type of high blood pressure that affects only the lungs and, in turn,

the right side of the heart. This happens when the small arteries of the lungs are underdeveloped, narrowed and thickened or blocked. This affects the structure and function of the arteries and vessels by increasing blood flow into open arteries resulting in uneven distribution of blood flow. This forces the heart to work harder. Eventually, the heart may weaken and fail. Though this condition is not curable, treatments are available to lessen the symptoms.

## What interventions are available to help the child with CDH breathe?

Depending on the child's individual circumstances, various treatments may be used to try and support a baby with CDH. Some of these include:

*High Frequency Ventilation* - a type of ventilation that provides a very fast breathing rate almost like a vibration. This therapy is used to reduce the ventilator-associated lung injury.

*Gentle Ventilation* - a type of ventilation used for pulmonary hypertension where high pressures are not used. This therapy is also used to reduce lung injury that can result from high ventilation pressure.

*Partial Liquid Ventilation* - a therapy where the lungs are filled with a special fluid that has anti-inflammatory properties and that prevents the alveoli from collapsing. Used with a standard ventilator, this method opens up the alveoli and delivers oxygen to parts of the lung that otherwise would not get it. This intervention is not in common use and is only available in few research centers in the U.S.

*ECMO* - Formally known as Extra Corporeal Membrane Oxygenation, this is

### ADRIENNE'S STORY

*By Jenn Dumas*

Back on that fateful day in April of 1996 when CDH tersely entered my life, I was a 22 year-old newlywed thrilled to be expecting my first child. My husband, Gary, and I were both healthy and young, with no genetic health conditions to be concerned about for our unborn child. We did not want to know the sex of the baby before it was born, and an ultrasound was not covered by our medical insurance. I could find no good reason

*“I knew that I would love the baby no matter what...”*

to have an ultrasound. I knew that I would love the baby no matter what, and I didn't care if it had Down Syndrome. At the time, that was the worst case scenario that I could envision. Having a few more years of wisdom under his belt and having watched his first wife suffer multiple miscarriages, Gary encouraged me to schedule the ultrasound. And so it began...

The face of the ultrasound technician glowed against the computer screen, where Gary and I caught our first glimpse of the miracle we had created. We reminded the technician that we did not want to know the baby's sex, and we joyfully whispered to each other in the dark room about the tiny hands and adorable profile of our baby.

a method of life support that circulates the blood through an oxygenating system, temporarily bypassing the heart and lungs. Typically, ECMO is used for short periods of time due to its risks and side effects.

*Nitric Oxide* - A gas that relaxes the blood vessel wall allowing increased blood flow as a treatment for pulmonary hypertension.

#### Summary

We now know that CDH is not simply a problem in the formation of the diaphragm. It is also accompanied by abnormal development of the lungs which interferes with gas exchange. Future research will focus on understanding the mechanisms of abnormal lung development in the hopes of developing early interventions and treatments for conditions like pulmonary hypertension and pulmonary hypoplasia. ■

### Do You Know Any Multiplex Families?

Did you know that families that have more than one member with CDH are particularly helpful to a genetic study like ours? Using powerful technologies we are able to identify CDH-causing mutations with greater ease. This information may be crucial in helping find answers for families with one individual with CDH. So keep spreading the word about the study!

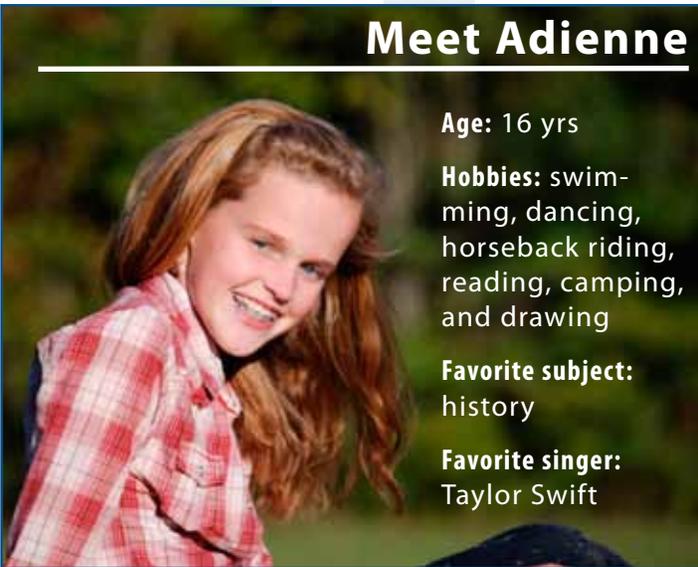
Abruptly, the technician dropped the Doppler she had been using to see our baby and left the room looking distraught, without a word to us. Must be personal issues, I thought. But when she returned with our obstetrician at her side moments later, I looked into two sets of teary eyes and knew that those tears were for us. I found myself listening to words describing a condition I had never heard before: Congenital Diaphragmatic Hernia. At 20 weeks gestational age, all of our baby girl's abdominal organs had developed in her chest. Her heart was displaced, and her lungs were unable to grow in part because they were being squished by the abdominal organs that were stuck in her chest and growing where they did not belong. There was no chance for survival given the severity of the birth defect at this gestational age. In a state of numbness, we were whisked out the door and down the street to a specialist who confirmed the diagnosis and prognosis and encouraged an immediate termination of the pregnancy. She explained that bringing a child in this condition into the world would require medical intervention. If she didn't die at birth, her life might be able to be prolonged in a veg-

etative state that would cost a lot of money and would require us to make the excruciatingly difficult decision to take her off life support. She said it would be selfish of us to continue with the pregnancy because of the suffering our baby would have to endure in a battle she couldn't win. She said it would be better to terminate this pregnancy and start fresh.

*“Specialist...said it would be better to terminate this pregnancy and start fresh.”*

Having been born with a strong will, (not to mention red hair), I was used to being accused of being defiant, but I never regretted following what my heart told me to do. The core of my soul knew not to terminate the pregnancy, despite the medical opinions we had received. In a dream I had on that first night, I saw a little girl with strawberry blond curls gently moving in the breeze while she was happily swinging on a swing set. We gave her a name, Adrienne Dale Dumas, and I made a pact not to cry during the pregnancy. I wanted Adrienne's environment to be that of positive energy. I willed every ounce of strength I had into the developing child inside my own body, and I looked forward to the day when I would see her on the swing set like I had seen in my dream. Gary was terrified, and could not understand how or why I could justify going against the advice of two sets of doctors. He knew his young wife had a mind of her own, but as

## Meet Adienne



**Age:** 16 yrs

**Hobbies:** swimming, dancing, horseback riding, reading, camping, and drawing

**Favorite subject:** history

**Favorite singer:** Taylor Swift

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newlyweds, we had not seen much of life together yet, and he wasn't as sure about this as I was. But I was unbendable, and he loved me enough to hold on tight and put his trust in me.

Research over the next week led me to a man named Jay Wilson, MD., at Boston Children's Hospital, who had made it his life's work to save Congenital Diaphragmatic Hernia (CDH) babies. When I sat in Dr. Wilson's office for the first time, I had all of the doctors' reports from Maine, and the ultrasound on DVD for him to view, but he simply tucked it in the file and said he didn't need to look at it. He told me that his experience had taught him that predictions about the chance for survival could not be based on the severity of the CDH birth defect during gestation. He told me to bring him a big, otherwise healthy, full-term baby when it was time to deliver, and he would do his best to save her for us. He showed us pho-

*"...[my husband] could not understand how or why I could justify going against the advice of two sets of doctors."*

tos of his former patients with such pride. They were beautiful children who had been born with CDH and had gone on to live normal lives. But he also told us that 50% of these babies died, even when their CDH defect had been so minor that it was missed on ultrasound. I have trouble remembering all of

the details from the time Adrienne was born until she was around 3, but I hear I handled it remarkably well (no, I was not medicated, drunk, or taking illegal drugs. Apparently "post-traumatic stress disorder" manifested in a way that caused

*"...I have trouble remembering all of the details from the time Adrienne was born until she was around three..."*

me to lose many of the memories). Despite all of the lengthy hospitalizations, life-support, months of ventilators, so many treatments (some not approved by the FDA), the 18 surgeries, her reliance on a feeding pump and oxygen for survival at home, all of the therapies, etc., etc., it was the feeding tubes she needed that broke my heart more than anything else. The surgically placed feeding tubes she needed signified that I was unable to provide for my baby daughter's very basic needs. I couldn't hold her, change her diaper, dress her, bathe her, or nurse her as I had looked forward to, and those were things I wasn't prepared for. I remember being very irritated with one of her nurses who was unwilling to let me dress my baby one day during her first few months in intensive care. Adrienne, of course, was lying under a heat lamp and was plenty warm enough, but a newborn baby doesn't belong naked and lying flat with tubes and lines coming from every God-given & medically created orifice on their body. I began to cry angry tears about it. I told her that it felt like my baby needed her more than she needed me. The nurse's misty eyes met mine, and she said that my baby needed to feel my love and strength through my presence, but at that point in her life, she needed medical intervention more than she needed my nurturing in order to survive. That time,

## A CHRONOLOGY OF LUCAS' STORY

*By Julie Durrant*

and the very few other times I cried next to Adrienne's bedside, her stats would show signs of distress, further proving that she needed me to stay positive so that she could be at her best. She needed me very much, just not in the way I had envisioned on the day the pregnancy test came back positive.

By the time Adrienne was seven years old, she was completely tube-free, was eating on her own (which was quite a struggle), and was left only with a road map's worth of scars on her abdomen and cold-induced asthma symptoms in the wake of this thing we call CDH.

Today she is a sometimes sassy 14-year old who still looks to me for strength and perspective, even though her current developmental stage causes her to push the envelope frequently. She is growing up as her very own person, with self-confidence, and a wide variety of interests, pursuits, talents, and abilities. She is very smart, loves her horse Tess, and will go far in life. At times when she is feeling weak and defeated, I remind her that at her young age, she has fought and won a battle that most adults are never faced with, and of those that are faced with such a battle, many don't win. And that is something that can put life's day-to-day challenges back into perspective in a snap. ■

### Wednesday December 3rd 1997

I was going for my 34 week check up before taking a trip for one last weekend break! I was feeling fine although my urine showed traces of protein & blood. I remember asking "Is everything ok?" My doctor replied "It's ok - see you at 41weeks".

### Sunday December 14th 1997

**3:30AM:** My water broke in bed. In a panic, Peter flew out of bed straight to the phone. I was a lot calmer! We arrived at the maternity ward at about 04:45am. Still quite calm, the examination confirmed a definite membrane rupture, and the CTG showed a sleepy trace. ("Not surprised" was my answer, as it's too early in the morning and I am not due for nearly 6 weeks!). Well that was the start of our son's fight!

**10:00AM:** Examination confirmed that I was 6 weeks early. CTG showed variability with decelerations. A drip was put in for a drug to induce labour - that hurt more than labour pains as I was only 2cms dilated!



Lucas soon after birth

## Thank you CHERUBS!

We would like to express another "thank you" to CHERUBS for their kind donation of \$10,000 to our CDH Study. The money came from CHERUBS' Research Fund. This donation provided support for animal models, as well as support for genetic analyses on affected patients and their families. Thank you to all who donated!

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**1:30PM:** Doctors decided to perform a caesarean section.

**2:13PM:** I heard one cry and was then told, "You have a boy, 1.528kg". I wanted to hold him, but they needed to do their checks. I caught a quick glimpse of him before he went to the SCBU. I think Pete went for a while, as I needed to be sorted out!

**3:00PM:** A nurse handed me a picture of our little boy; I was still unaware of the road he would need to take.

**6:30PM:** The doctor came to see me and asked where Pete was. I told him he had gone home for a while as it had been a LONG DAY. The Dr. left, but a wave went through me - I knew something must be wrong. Pete arrived back asking what's wrong, but I couldn't speak and just shrugged my shoulders. Soon, several doctors came into the room holding an x-ray. Their words were saying, "your son has a left sided diaphragmatic hernia and needs to be in a specialized hospital to perform an operation, etc." I just kept thinking, "This wasn't happening!"

Our first child. This is a dream. How can this be?" My left side just started to shake and I couldn't control the shakes. I asked to see our son before he got in the ambulance. I held him briefly, had a photo taken. He was so, so tiny, but perfect. I touched his fingers all silky and smooth. A light kiss to his forehead, whispering, "The angels are coming to take you away and I will see you in the morning".

*"I just kept thinking -this wasn't happening! ...This is a dream"*

## Monday December 15th 1997

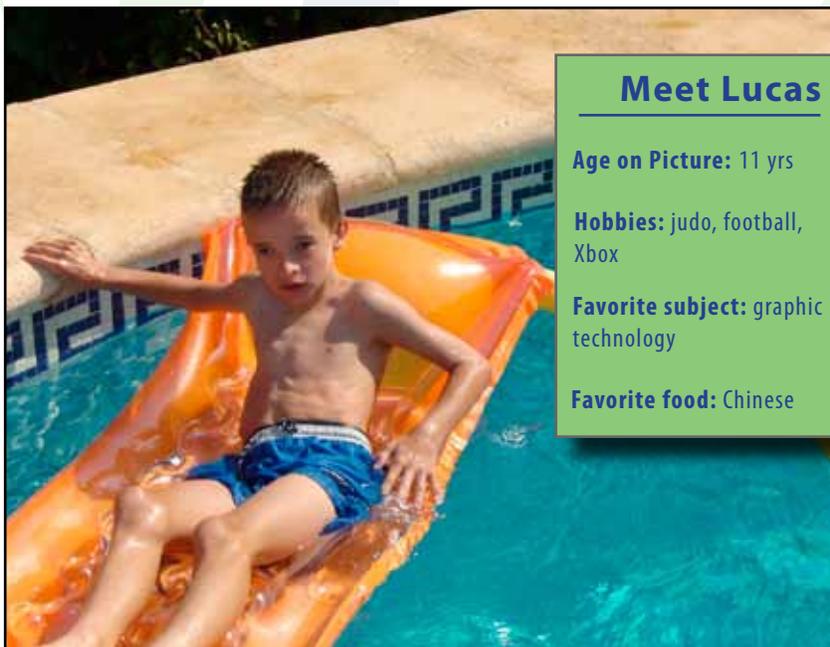
**Morning:** What has gone on? There are babies crying, and there is laughter as new life is being born. Where is our son? Not with his mother. Could this all just have been a horrible dream?

**Afternoon:** I arrived at the John Radcliffe Hospital in an ambulance early afternoon on the 15th of December. Pete followed the ambulance. When we arrived, he pushed me in a wheelchair down to neonatal intensive care unit, machines beeping as we entered and our son lying motionless with tubes and wires coming out of him. This is our baby so ill, but fighting to survive. The nurses were there tending to him and then the doctor arrived explaining the operation will be performed on the 16th December and giving us a 50/50 chance

of survival. Everyone was so kind and we knew our son was in the best care and prayed he would survive. The nurses helped us to name our boy. The name Lucas was decided, meaning LIGHT.

## December 1997 - January 1998

The operation was a success and the surgeon even noted a bit of a lung on the left side. Lucas was out of intensive care and transferred back to our local hospital on the 29th December. On the 14th January 1998, Lucas came home for the very first time!



## Meet Lucas

**Age on Picture:** 11 yrs

**Hobbies:** judo, football, Xbox

**Favorite subject:** graphic technology

**Favorite food:** Chinese

## February 1998

On February 5th, Lucas wouldn't stop screaming. A bulge below his tummy to the right was why he was screaming, so I rushed Lucas back to the hospital. It was an inguinal hernia which they pushed back but gave us a letter to the John Radcliffe if it pops back out. Yes it did, so on the 10th of February both sides were repaired as his surgeon didn't want the other side to go later! Two operations in 7 weeks! His surgeon didn't want to perform any more just yet!

## Since the Newborn Period ...

Looking back, Lucas' first three months were a blur - like a dream but one that was happening to someone else. But Lucas is now 12!! He has already gone through so much during the first 12 years of his life - a lot of operations and procedures, so many medical complications, etc., Lucas not only had diaphragmatic hernia but also had ambiguous genitalia (with hypospadias and undescended testes). He had to endure HCG injections three times a week for six weeks hoping this may bring down his testes as they were still in the abdomen. This unfortunately wasn't successful so in February 2000, Lucas had his first repair of his hypospadias.

*“Given his history, I am amazed at how well Lucas is doing!”*

Feeding was a nightmare. Lucas would arch his back and go rigid on his milk feeds, followed by projectile vomiting and his lips turned blue. When he was little, Lucas was put on medications to treat possible reflux. Recently he was diagnosed with a severe case of reflux and new medications are being started. Duocal was added to his feeds although weight is still a major problem. In April 1999, he was started on nasogastric feeds because of poor weight gain. The tube was constantly coming out and we had to make frequent trips back to the hospital for it to be re-inserted. An upper GI series showed

that his stomach was slow to empty and that his bowel motility was not great.

Lucas also has been diagnosed with moderate to severe bilateral mixed hearing loss and requires hearing aids. Awaiting us in the future is eye surgery for a “squint” (strabismus or lazy eye) in both eyes, as well as another surgery for hypospadias repair.



Lucas with his Sister

Given his history, I am amazed at how well Lucas is doing! He attends mainstream school (although bullying has been a problem throughout, and recently he has significant problems with dyslexia, dyspraxia, and sensory integration issues). Lucas is a kind gentle boy and, as you can see from the photos, is relatively healthy. Lucas's list of things that have happened may seem long, but we all take pleasure and remind ourselves what might have been and enjoy each day and have lots of fun! Lucas has a healthy younger sister who was born 21st December 1998, and as a family we cannot express the depth of our gratitude to all the experts who are helping us with our son. Since his combination of health issues seems unique and a bit puzzling to our doctors, we participate in ongoing research studies both here in England and in Boston. We hope this will speed up the process of finding answers not only for Lucas but for others, too. ■

