



April 2008

Tenth Anniversary Edition

Kidneeds New Name, New Decade, Same Thanks

October 30, 2007 was Kidneeds' 10th birthday. Though there was candy corn on the counter rather than candied yams, it felt like Thanksgiving. Every day brings a reason for us to give thanks to all of you for making a fragile hope, a likely reality. Thank you for walking beside us on this incredible journey. You haven't been well wishers, but active participants, enabling us to move towards a treatment. Your support of our family or the DDD family that you are connected to is an incredible gift. There is no greater hope for Jenna than seeing an active team at the Chili Dog Fair or Enchiladafest helping to change her current course. It is in the journey that many little miracles happen, and many have happened the past 10 years.

It is sometimes hard to explain all the complicated scientific advances. But at least the name of the disease is easier to say. You will see in the progress notes that the name MPGN 2 has been changed to Dense Deposit Disease: DDD, that's easy!

We have found that many of the initial theories explaining the cause of DDD were inaccurate or incomplete; but mostly we found we were dealing with the unknown. Experts told us that it would require tens of millions of dollars to get started and to get any where. But the experts didn't consider the impact you have made. You have helped us with fund raising. Many patients and their families have participated in research studies. And count-

less doctors, nurses and scientists have volunteered their time, their own resources and their knowledge so that we could highly leverage every donation received by Kidneeds to support the many grants we have awarded. We have raised over \$1,000,000 but we have received much more than that in volunteer effort and support.

This anniversary edition is a time line of major events of the past 10 years. The other day Richard was excited about a new research finding and mentioned that we should contact Hollywood and sell film rights to the story to help fund the final leg of the DDD journey.

It is a tremendous story on or off screen. It has all the elements of those true-life movies with endings that have you grabbing for the last popcorn-scented napkin: tragedy, triumphant courage, around-the-clock work, stand-with-you-in-the-trenches friendships, strokes of good luck, and in the end, we are sure, success. We still await this final scene, and as we wait, we give thanks to all who have been a part of the Kidneeds' cast the past 10 years.

Lynne and Richard



1997



2007



Special points of interest:

- For more information on Kidneeds, please visit www.medicine.uiowa.edu/kidneeds
- For patient information, fundraising and the MPGN Database please email Lynne Lanning at kidneedsmpgn@yahoo.com
- For research or grant information contact Richard Smith: Richard-smith@uiowa.edu

Dreams, Teams and Fusion Proteins

The Dream



Judges at the Chili Dog Fair



Mark Dreusicke of Toyota of Iowa City Football Skills and AXO Volunteers



Chili Dog Fair Bake Shoppe



Jenna Smith & Sunny Layne of KWWL TV



Magical Lemonade Stand

Kidneeds was founded in 1997. At that time, we knew of only two other families who had daughters with Membranoproliferative Glomerulonephritis type 2 (MPGN2). Both girls, like Jenna, were in kidney failure. Not surprisingly, there were no support groups or networks for families with MPGN2, and there was almost no biomedical research on this disease.

After all, what was the point in studying a disease that affected only a few patients? Without large numbers of patients, meaningful data are difficult to obtain and without meaningful data, research funding from the Federal agencies like the National Institutes of Health (NIH) is impossible to get. Rare diseases are defined in the USA as diseases that affect less than 6 persons per 10,000, and MPGN2 affects about 1 person per 1,000,000, making it rare even among rare diseases. No scientist had ever been awarded an NIH federal grant to study MPGN2.

Clinical studies had been conducted on MPGN2, but in all of these studies, MPGN2 was grouped with other types of glomerulonephritis, most frequently with MPGN1 and MPGN3, to boost patient numbers. On this basis, steroid therapy was established as the treatment of choice for children with MPGN1, 2 and 3. Steroids, like Prednisone, act systemically to depress the immune system.

Unfortunately, although the grouping of MPGN 1, 2 and 3 suggests a family of diseases with implied similarities in cause and treatment, this grouping turned out to be deceptively inaccurate. We learned that there was no clear understanding of how MPGN2 was caused and there was no clear understanding of why the kidneys were destroyed. Any genetic contribution to the disease remained a mystery and even the composition of the dense deposits which develop in the kidney were unknown. The natural history of MPGN2 in children and

adults was unclear.

Most distressing of all was an appointment we had with a leading pediatric nephrologist that concluded with the admonition that “nothing new has been learned about this disease in 40 years and nothing new is going to be learned about it in another 40, barring something unforeseen”. Kidneeds was that unforeseen factor.

Kidneeds was chartered as a unique granting agency with 501c3 status under the umbrella of the Greater Cedar Rapids Community Foundation. Unlike all other granting agencies we are aware of, 100% of all donations go to MPGN 2 research. Any administrative costs are paid privately. In addition, Kidneeds has no fundraising arm - all money comes from volunteer efforts to benefit Kidneeds.

Once chartered, Kidneeds had to tackle two objectives: first, to raise money to support this research; and second, to identify and entice outstanding scientists to study a complex, rare disease. The long term goal was to find a treatment – a ‘cure’ – for MPGN2 and since Kidneeds would have only limited resources, we decided that we should try to support numerous small grants with the hope that this ‘seed’ money would make it possible for some scientists to compete successfully for larger sums of money like the Federal grants offered through the National Institutes of Health. Raising money and identifying scientists was the beginning of Kidneeds’ real story.

The Teams

In December, 1997 we asked family members to give donations to Kidneeds instead of Christmas presents, as we saw the Kidneeds effort as a family endeavor. But when friends heard what we were doing, they changed the scope of Kidneeds from a family mission into a major grassroots effort to find a treatment for patients with MPGN2. In 1998, friends and family ran marathons for Kidneeds in Houston and Austin, Texas; Betsy Boyd and Evelyn Weirich started the now famous Cinco de Mayo Enchiladafest; and Joy Baker, Mike Welsh and Art Johannes joined efforts with

the 'Dressage in the Heartland' and the first chili cook off. The next year the event morphed into the Chili Dog Fair when Kay Klein, Sue Ann Thompson, and the Iowa City Dog Obedience Club and the Hawkeye Kennel Club took over after Joy moved.

To attract scientists, we reviewed all of the available papers on MPGN2 and sent out personal letters to all authors notifying them of Kidneeds, its mission, and the opportunity for funding. We also advertised in prominent medical journals like the Journal of the American Medical Association, and wrote to every nephrology training program in the nation. And in 1998 we made our first award and funded a grant submitted by Dr. Charles Alpers.

In 1998 Kidneeds also got a website. Richard created it and while web design is not his strong point, the site became a contact point for MPGN2 families. In the first few years, if we were in contact with one or two other families with MPGN2 in a year that was remarkable. But the families that did contact us became part of the Kidneeds story. The Personte and Potter families in NY and PA, respectively, began fundraisers, and the Personte Annual Golf Tournament is still going on. To help with the tremendous amount of work we faced, especially with fund raisers in Iowa City and Johnson County like the Chili Dog Fair, the AXO sorority 'adopted' Kidneeds and has helped us ever since.

Kidneeds now receives several grants every year that must be evaluated for scientific merit. To evaluate these grants without bias, Kidneeds established a Board of Scientific Advisors made up of prominent scientists throughout the United States; no family members of MPGN2 patients were on this Board. Each grant was reviewed by three scientists and an average score was determined. Scores were then reviewed by Kidneeds Board of Directors, which decided how much money to award each year to the most meritorious grants. As Figure 1 shows, Kidneeds has awarded over \$750,000 to scientists around the world since 1998.

In 2001, the National Kidney Foundation of Iowa and private funds were used to create 'The MPGN Database' at the University of Iowa, College of Nursing. The purpose of the database was to collect epidemiological information on patients with MPGN2. With the extensive help of Drs. Ann Marie McCarthy and Der Fa Lu, both at the College of Nursing, 'The MPGN Database' became a reality.

The Database tackled important questions that desperately needed to be answered. Amazingly, we still had no idea of the 'profile' of a patient with MPGN2. We didn't know why some patients had a rapid and aggressive disease course while others did not. We didn't know whether steroid therapy, recommended so many years ago, really did anything at all. And most important of all, we didn't know whether transplant success was worse for MPGN2 as compared to other kidney diseases. Each question seemed to generate 10 more questions. By this time, we knew 15 families with MPGN2 and so we started to ask them these questions.

2004 was a watershed year. We were approached by Sean and Hope Tully, whose young daughter had been diagnosed with MPGN2. The Tullys suggested that we hold a conference and invite scientists who had some understanding of MPGN2 to attend and share their ideas. Perhaps by putting together these ideas, a clearer picture of MPGN2 would emerge. Although we had considered a conference earlier, Kidneeds' charter to give 100% of all donations to research meant that we would need an alternate funding source to make a conference possible. The Tullys generously offered to fund this conference and established the Milagros Research Fund for that purpose. That year, Dr. Richard K. Miller, President of Olin College of Engineering hosted the first MPGN2 Focus Group meeting on Olin's



Sean and Hope Tully



Drs. Smith, Lim and Oetting at Dr. Lim's Chinese Fire Pot Dinner for Kidneeds

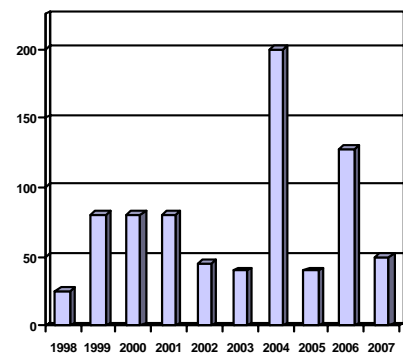


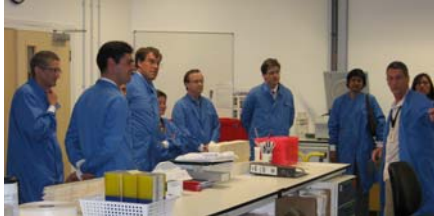
Figure 1. Kidneeds has raised just over \$1,000,000 and has made grant awards from 1998-2007 totaling \$768,000. Kidneeds funding has been acknowledged in over 30 scientific articles.



2004 DDD Conference, Olin College



2006 DDD Conference, Hinxton, UK



2006 DDD Conference scientists tour a sequencing facility at the Sanger Centre, Hinxton, UK



Richard and Fabrizio Spoleti discuss plans for a meeting at the Mario Negri Institute, Bergamo, Italy, in February, 2008.

Campus. The conference was supported by a small grant from the NIH (NIDDK) and the generous support of the Tully's Milagros Research Fund.

Over 20 scientists from around the world met for a weekend "brainstorming" session. A variety of presentations were given and at the end of the meeting, we left invigorated and enthused with the conviction that MPGN2 was a complex problem but one that could be solved. The conference also resulted in the creation of a collaboratory – a laboratory without walls – where scientists funded by Kidneeds would share data to quickly advance our knowledge of MPGN2. The consensus article written as a result of this conference (Membranoproliferative Glomerulonephritis Type II (Dense Deposit Disease): An Update. *J Am Nephrol Soc* 16: 1392-1403, 2005) became one of the Journal's most read articles. Spurred by the MPGN2 Focus Group meeting, Kidneeds received a large number of grant applications and gave out awards totaling \$200,000 in 2004.

In planning the first MPGN2 Focus Group meeting, Richard found himself at the initial stages of his own scientific involvement with MPGN2. Following the conference, he began to apply his background in human genetics to MPGN2. No funding was available for this research and applying to Kidneeds was clearly a conflict of interest. Nevertheless, a small group of people in Richard's lab began to chip away at the MPGN2 problem.

In 2006, Kidneeds held its second focus group meeting. The venue was The Sanger Centre, located in the small town of Hinxton just outside Cambridge, England, where much of the human genome had been sequenced. The meeting was selected as an invitation-only 'Conference of Excellence' and was supported by the Wellcome Trust, the National Institutes of Health (NIDDK) and the Milagros Research

Fund. The rigorous scientific schedule included talks on the characteristic pathology of MPGN2, the cause of the disease, its genetics, and of direct relevance to clinicians, diagnostic strategies and possible treatment considerations. Again, a consensus article was written by the group: 'New approaches to the treatment of Dense Deposit Disease' (*J Am Soc Nephrol* 2007 Aug 5 [Epub ahead of print]; 18:2447-56, 2007). One of the first things you'll notice in reading the title is the lack of any reference to MPGN2. The group recommended using the name Dense Deposit Disease (DDD) instead of MPGN2 to reflect the fact that DDD is NOT like MPGN1 or MPGN3 and is, in fact, a distinct disease characterized by dense deposits in the kidney. The paper focused on the clinical evaluation and treatment of patients with MPGN2 and proposed a system that clinicians could use to establish efficacy of treatments for DDD as these come available.

The Fusion Proteins

How has Kidneeds fared as "that unforeseen factor" over the past decade? For one, Richard and two other scientists have received a grant from the National Institutes of Health, the first ever awarded to study DDD. The focus of this grant is on the genetics of DDD.

What has Kidneeds achieved? What do we know about DDD that we did not know 10 years ago? Well, for starters, we know the cause of DDD – uncontrolled activity of a protein complex called C3 convertase (or C3bBb for short). In you, in me, in anyone, if activity of C3 convertase is allowed to go unchecked, membranes in the glomeruli, the filtering units of the kidneys, will be destroyed and your kidneys will fail. Similar membranes in your eyes, called Bruch's membrane, can be damaged with the onset of vision problems. We have also learned that uncontrolled activity of C3 convertase can be triggered by a variety of factors. Clear genetic factors have been identified. For example, mutations in a gene called Complement Factor H (abbreviated CFH) can lead to uncon-

trolled activity of C3 convertase and DDD will then develop. We now recommend that all patients with DDD get mutation screening of this gene. To help clinicians around the country, this screening is provided for free in the Clinical Diagnostics Division of Richard's lab. Dr Greg Hageman, a participant at both DDD Focus Groups meetings, is also making pure CFH to see whether this protein will be effective as a medical treatment for some patients with DDD.

In addition to CFH, we have studied a large number of other genes in patients with DDD and have found that variations in six of the genes we have studied increase a person's odds of getting DDD. But getting DDD still requires a trigger, perhaps a cold or a viral infection, and this trigger remains to be identified.

We have used a laser beam to cut the dense deposits and filtering units out of kidney biopsy samples in patients with DDD. These miniscule bits of tissue were then fed into a special machine for protein analysis. Some of the proteins we found in the dense deposits were expected, but there were also a few important surprises. One surprise was a protein called Complement Factor H Related 1 or CFHR1 for short. CFHR1 is very similar to CFH, and we believe this similarity makes it possible for CFHR1 to out-compete CFH for binding sites on membranes in the glomeruli of the kidney. Once there, CFHR1 is not as effective as is CFH in protecting the kidney from uncontrolled C3 convertase activity. The end result is DDD and eventual kidney failure.

While some of these ideas remain to be validated, they have prompted several laboratories to begin making medicines that may be helpful in the treatment of DDD. One medicine is called Sulodexide. It inhibits an enzyme called heparanase, which is present in the glomeruli of patients with DDD. Although we do not know whether using Sulodexide to turn off heparanase will help patients with DDD, the Federal government has given

the University of Iowa permission to use Sulodexide in a national study to see if it is helpful in altering the course of DDD. This study represents the first drug trial for DDD (ClinicalTrials.gov identifier NCT00583427; <http://clinicaltrials.gov/ct2/show/NCT00583427?term=Sulodexide&rank=1>).

Another drug called Eculizumab has recently been approved by the FDA for patients with a kidney disease called nocturnal hemolytic uremia. Eculizumab prevents a protein called C5 from functioning properly. Research done by Dr. Matthew Pickering, a scientist funded by Kidneeds, has shown that inhibiting C5 function with this type of drug slows the rate of disease progression in mice with DDD. Although Eculizumab has not been used in patients with DDD, these data suggest that a trial with this medicine is warranted.

A novel medicine under development for DDD is a fusion drug that links pieces of two different proteins that are normally present in people but not joined together. One portion is predicted to "stick" to kidney glomeruli and the other portion is predicted to inactivate C3 convertase. We hope this novel protein will help patients with DDD by "sticking" to their glomeruli and inactivating any C3 convertase that is also there. While we don't know if this medicine will work, the concept is reasonable. We have made the mouse version to see whether this medicine will make mice with DDD better. If it does, we will make the human version.

And the patients with DDD, what have we learned about them? Nearly 100 patients with DDD have now enrolled in 'The MPGN Database', making this database the largest on DDD in the world. From it we have learned that DDD is a more aggressive disease in younger patients and that progression to renal failure and dialysis typically occurs within 5 years of diagnosis. Of patients who have had DDD for at least



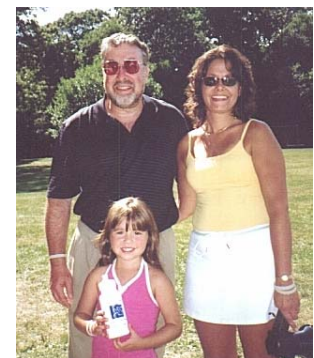
Evelyn and Frank Weirich



Luncheon benefit for Kidneeds Committee in Chappaqua, NY.



AXO Volunteers



The first marathon/walk for Kidneeds organized by Michele Stumpf and family in CT.



Parents and fundraisers, Carol Personte (left) and Cindy LaTona

10 years, half are in renal failure and require dialysis. And of patients who have had transplants, half have lost their new kidneys to recurrent disease. These statistics are very sobering and speak to the urgency of a treatment for DDD. Fortunately, Kidneeds' funded research by Dr. Jessy Alexander has shown that the dense deposits in the kidneys of mice with DDD are reversible. This finding suggests that if treatments are initiated before kidney scarring takes place, kidney function can be saved. And so it is with treatments in mind that we are looking ahead to 2008.



Isshinryu Kickathon

One of the important contributions made by the 2007 article in the Journal of the American Society of Nephrology was to provide clinicians with a diagnostic approach to the evaluation of a patient with DDD. State-of-the-art diagnostics, including mutation screening of CFH and obtaining baseline assessments of complement activity, were recommended.



DDD Family Conference

Also included was an integrated approach to treatment that included references to Sulodexide, Eculizumab and plasma exchange. This diagnostic and treatment algorithm was highlighted in Nature – Clinical Practice Nephrology 3:640, 2007 (<http://www.nature.com/ncpneph/journal/v3/n12/full/ncpneph0645.html>). While these medications offer a starting point, it is doubtful that any one will be the "cure" we are looking for.



The Ninth Weirich and Nusser Enchiladafest

The development of novel treatment strategies based on new genetic findings and our present understanding of the complement derangements in DDD will be the subject of the third DDD Focus Group meeting in August, 2008. Kidneeds has been awarded a second Wellcome Trust grant and so this will be our second Hinxtion 'Conference of Excellence'. Like the other two conferences, it will be by invitation only and will allow scientists from different fields to brain-storm about the devel-

opment of effective treatments for DDD.

As therapies are proposed, each therapy must be evaluated in an unbiased way to determine whether it is effective as a treatment for DDD. This task is monumental when we are talking about a disease that affects only 1 person per 1,000,000. Certainly, no physician can amass sufficient experience with DDD to know what medicines are effective. To overcome this obstacle and to facilitate the evaluation of therapies in a real-time, the Dense Deposit Disease Outcomes Database (DDDOD) has been established through the College of Engineering at the University of Iowa under the direction of Dr. Tom Casavant. This secure site provides a format to allow physicians to share data and outcomes in real time. Through a collective and shared experience in treating DDD, a knowledge base can be established to evaluate promising therapies in the shortest amount of time possible.

We are convinced that a treatment for DDD will be available within the next 5 years, if not sooner. The successes that Kidneeds has achieved and the optimism the future holds for patients with DDD because of Kidneeds are simply miraculous. And it is a triumph that reflects not the actions of a few people, but rather the enormous commitments of time and money made by many, many people around the world. Ninety-nine percent of the people who have helped on this journey know only one person - if any - with DDD. As William Feather once said, "Something that has always puzzled me all my life is why, when I am in special need of help, the good deed is usually done by somebody on whom I have no claim." This is true for our family and the other families with DDD. There is simply no adequate way to say thank you to all who have had a role in making Kidneeds the unforeseen factor it has become and making it possible to come so far in so short a time.

Fundraisers

2007

Eighth Golf Tournament for Kidneeds organized by Carol Personte and friends in Webster, NY.

Isshinryu Karate Academy Kickathon in honor of Krystin Wheeler.

The Stumpfs held their Third Walkathon for Kidneeds in CT.

The Weirich and Nusser Families with the help of Plaza Auto Auction hosted the Ninth Enchiladafest.

The Ninth Chili Dog Fair was held in September along with the second DDD Family meeting.

Chameleon Cache and Hands Jewelers have continued to sponsor Jenna Smith's jewelry.

2008

Hope Tully organized a dinner, dance and silent auction in London, England March 8, 2008.

Carol Personte will hold the 9th 'Golf for Kidneeds' golf tournament in Webster, NY on Sept. 14. Please contact her at: cookiefool@frontiernet.net

For other fundraisers, visit the Kidneeds website for specific information.

As there are strict fundraising guidelines, please speak with Lynne before doing any fundraisers that will involve the Kidneeds name. Also you will need to contact Josie Velles (319-366-3862) at the Greater Cedar Rapids Foundation prior to any fundraiser to make sure you are in compliance with their guidelines and so they are aware of the money that may be coming into the Kidneeds account.

Kidneeds uses 100% of all donations for research directed at finding a cure for Dense Deposit Disease.



Mowing for Kidneeds



Richard with Randi and Gary Levitz, donors and advisors.



Fran (left) and Hope at the Kidneeds Luncheon Benefit 2005



The second Johnson County Medical Society Alliance for Kidneeds.



Gabrielle Personte's uncle, dad, grandfather and friend swing for a cure at the 8th Webster, NY Golf Tournament

Where have grants come from?

Over the years these donors have given or raised enough to fund at least one \$40,000 grant. Some donors prefer to remain anonymous.

The Gary and Randi Levitz and Lee and Mary Noel families

Carol Personte and Pat Gross; Golf Tournament, NY

The Weirich/Nusser Enchiladafest

The Chili Dog Fair

The NY Luncheon Fundraiser

The West LB Cocktail Fundraiser

Toyota of Iowa City and Kathy and Mark Dreusicke

The Jeremy Smith Family

The Richard Smith Family

The Rodney Smith Family

The Sean Tully Family

We are thankful to all donors. Many of our donations come in small dominations; each donation is so important and all donations bring us closer to a treatment.

Memorials were given for Dr. Stephen Noel, Zachary Stanley's grandfather, Gerald Schmidt and Patrick Crockett's Grandmother, Mrs. Edith Sittington, Susan Liston and Rodney Smith.

Gifts were made in honor of Diane Dreusicke, Sarah Jandik, Dean and Dorris Lanning, Nicholas LaTona, Randi and Gary Levitz, Jenna Smith, Richard Smith and Christopher Stuhlman.

DDD Family Meetings

In September 2006 and 2007, we held DDD family meetings. These meetings brought families together to share questions and concerns. We also gave updates on research, treatment and disease findings. These meetings are a nice way for patients and their families to discuss issues unique to DDD, as well as issues with dialysis and transplantation. If you are interested in attending a family meeting in 2008 or 2009, please contact Lynne at: kidneedsmpgn@yahoo.com. If you are a student on dialysis and are willing to answer a questionnaire on how you manage studying, extracurricular activities and dialysis please e-mail Lynne. She will send you an electronic survey to fill out. We have an increasing number of students of all ages (elementary to college) who are on dialysis and would like to know how others deal with the same situation.

Kidneeds, Inc. is a non profit corporation that is a fund of the Greater Cedar Rapids Community Foundation (GRCRF). Our 501 c3 tax deductible status is derived through the GRCRF.

Donations can be made to: Kidneeds, GRCRF

Mail to: Greater Cedar Rapids Community Foundation
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Cedar Rapids, Iowa 52404

For questions and Federal Tax ID numbers, please contact Josie Velles at 319-366-3682.

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