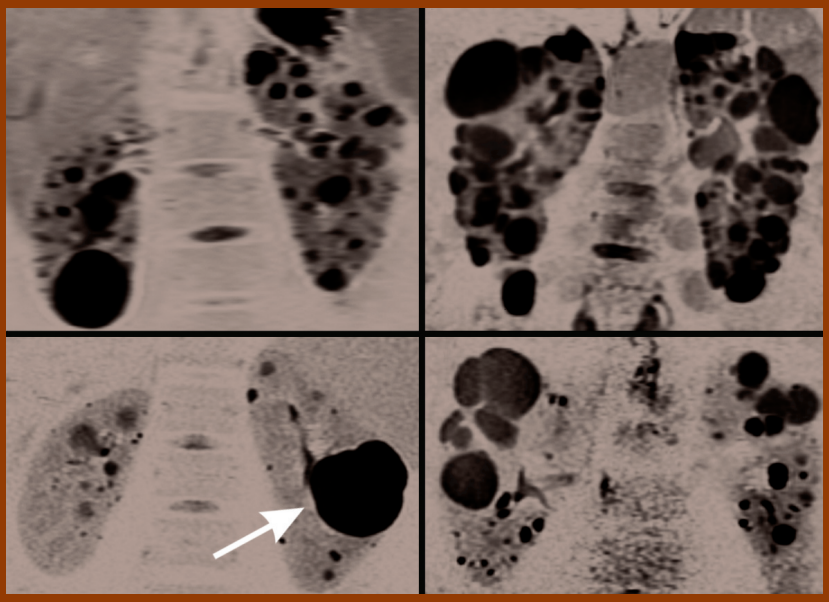

Polycystic kidney disease (PKD) manifests as fluid-filled cysts in the kidneys. These cysts can progress to the point of compromising kidney function, resulting in kidney failure. Through the Consortium for Radiologic Imaging Studies of PKD (CRISP), the NIDDK is supporting research into imaging techniques capable of measuring cyst and kidney volumes to improve monitoring of disease progression. These colorized magnetic resonance images show kidney cysts (black; see white arrow pointing to one of many cysts) in four PKD patients with different ages and genetic backgrounds who participated in a CRISP study described later in this chapter.

Image courtesy of Dr. Peter Harris. Adapted by permission from Lippincott Williams & Wilkins: Harris et al. Cyst number but not the rate of cystic growth is associated with the mutated gene in autosomal dominant polycystic kidney disease, Journal of the American Society of Nephrology 17: 3013-3019, 2006.

Kidney, Urologic, and Hematologic Diseases

Diseases of the kidneys, urologic system, and blood are among the most critical health problems in the U.S. They afflict millions of Americans, including children and young adults. The NIDDK is committed to enhancing research to understand, treat, and prevent these diseases.

Normal, healthy kidneys process about 200 quarts of blood a day to sift out about two quarts of waste products and extra water from the blood, excreting them as urine. In people with chronic kidney disease, the function of these life-sustaining organs is impaired. Kidney disease may progress to irreversible kidney failure, a condition known as end-stage renal disease (ESRD). People with ESRD require dialysis or a kidney transplant to live. As of 2004, there were 472,000 persons receiving dialysis or living with a kidney transplant.[1] Approximately 10 to 20 million people in the U.S. have earlier kidney disease.[2] The leading cause of kidney disease is diabetes, with hypertension (high blood pressure) the second-leading cause. If unchecked, the recent increases in obesity and type 2 diabetes in the U.S. will have grave implications in several years, as more people begin to develop kidney complications of diabetes.

Racial minorities, particularly African Americans, Hispanics, and American Indians, bear a disproportionate burden of chronic kidney disease. African Americans are four times more likely and American Indians are twice as likely to develop kidney failure as non-Hispanic whites. Hispanics have a significantly increased risk for kidney failure, as well.

The NIDDK supports a significant body of research aimed at increased understanding of the biology underlying chronic kidney disease. The chronic renal diseases program supports basic and clinical research on kidney development and disease, including the causes of kidney disease; the underlying mechanisms leading to progression of kidney disease to ESRD; and the identification and testing of possible treatments to prevent development or halt progression of kidney disease. Areas of focus include diseases that collectively account for more than half of all cases of treated ESRD. Of special interest are studies of inherited diseases such as polycystic kidney disease, congenital kidney disorders, and immune-related glomerular diseases, including IgA nephropathy and the hemolytic uremic syndrome. The National Kidney Disease Education Program, which is designed to raise awareness about the problem of kidney disease and steps that should be taken to treat chronic kidney disease and prevent kidney failure, represents a major educational outreach effort to patients and physicians.

Urologic diseases affect men and women of all ages, result in significant health care expenditures, and may lead to substantial disability and impaired quality of life. The NIDDK's urology research portfolio includes basic, clinical, and epidemiological research on the genitourinary (GU) tract. The NIDDK has supported studies in benign and noncancerous urologic disorders and diseases, including benign prostatic hyperplasia, prostatitis, urinary tract infections, urinary tract stone disease, interstitial cystitis, urinary incontinence, pelvic floor disorders, and congenital anomalies of the genitourinary tract, as well as erectile and sexual dysfunction.

Benign prostatic hyperplasia, or BPH, is a common, symptomatic condition that increases with age in men. Prostatitis—chronic inflammation of the prostate gland—is a painful condition that accounts

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[1] *U.S. Renal Data System, USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2006.*

[2] *Coresh J, et al., 2003. Am. J. Kidney Diseases 41: 1-12.*

for a significant percentage of all physician visits by young and middle-aged men for complaints involving the genital and urinary systems. In addition to a portfolio of research studies including both basic and clinical sciences, the NIDDK sponsors the Chronic Prostatitis Collaborative Research Network, a clinical network of research sites performing clinical studies on pelvic pain of prostatitis. The NIDDK is committed to enhancing research to understand, treat, and prevent these common and troubling disorders.

Infections of the urinary tract are extremely common in women, and many women suffer repeated urinary tract infections (UTIs). The NIDDK's portfolio includes both basic science, as well as clinical projects. Painful bladder syndrome/interstitial cystitis (PBS/IC) is a debilitating, chronic, painful bladder disease. The number of individuals suffering with PBS/IC is not known with certainty, but it has been estimated that 700,000 to 1 million adult women in the U.S. may have the disorder, with a gender predominance of women affected (90 percent). The NIDDK sponsors the Interstitial Cystitis Clinical Trials Group/Research Network to conduct clinical studies in PBS/IC.

A conservative estimate is that approximately 13 million Americans, most of them women, suffer from urinary incontinence. Many who have the disorder still suffer in silence due to embarrassment and lack of knowledge over options available. The clinical field of urinary incontinence has changed dramatically in the last decade with the advent of new surgical procedures that have rapidly been introduced into the field. The NIDDK's Urinary Incontinence Treatment Network has produced results. Two major clinical studies have just recently been completed and are currently being analyzed.

Urolithiasis and urinary tract stone disease are frequent causes of visits to health care providers. The NIDDK has a robust interest in this field, ranging from preventative health to basic stone formation/dissolution and treatment with improvement of the current minimally invasive treatment modalities of laser or ultrasound lithotripsy or extracorporal shock wave lithotripsy (ESWL).

One of the most common causes of kidney failure in children is vesicoureteral reflux. In fact, abnormalities of the genitourinary tract are among the most common birth defects. The NIDDK is conducting a clinical trial to determine if the current practice of long-term antibiotics is necessary for the treatment of these children.

The NIDDK's hematology research program uses a broad approach to enhance understanding the normal and abnormal function of blood cells and the blood-forming system. Research efforts include studies of a number of blood diseases, including sickle cell disease, the thalassemias, aplastic anemia, iron deficiency anemia, hemolytic anemias, and thrombocytopenia. The Institute is also keenly interested in the basic biology and genetic regulation of stem cells, especially adult hematopoietic stem cells, which are needed for bone marrow transplants and may have broader application in gene therapy research. An additional priority of the Institute's hematology research program is the development of improved iron-chelating drugs to reduce the toxic iron burden in people who receive multiple blood transfusions for the treatment of diseases.

ADVANCES IN CURBING CHRONIC KIDNEY DISEASE

Trends Show Success in Controlling End-Stage Renal Disease in People with Diabetes: End-stage renal disease (ESRD) is a costly and disabling condition that requires dialysis or transplantation for survival. It disproportionately affects racial and ethnic minority populations and is associated with a high mortality rate. Diabetes and high blood pressure remain the leading causes of

ESRD, accounting for 44 percent and 28 percent of all new cases, respectively. Data released by the NIDDK-supported U.S. Renal Data System (USRDS) indicate that rates of new cases of kidney failure have stabilized after 20 years of 5 to 10 percent annual increases. The reasons for improvement may be attributable, at least in part, to better prevention-oriented care. For patients with diabetes, the landmark Diabetes Control and Complications Trial established the importance of good control of blood glucose and the value of monitoring the urine for protein—an early sign of kidney disease. Other studies performed in the 1990s demonstrated that medications (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) could significantly delay or prevent kidney failure, particularly in patients with protein in the urine. Unfortunately, this good news does not yet apply across the entire U.S. population. Racial disparities still persist in the rates of ESRD. The NIDDK's National Kidney Disease Education Program (NKDEP) is tailoring science-based messages to groups disproportionately affected by kidney diseases in continuing efforts to address these disparities.

Burrows NR, Wang J, Geiss LS, Venkat Narayan KM, and Engelgau MM. Incidence of end-stage renal disease among persons with diabetes—United States, 1990-2002. MMWR Weekly 54: 1097-1100, 2005.

Impact of Overweight and Obesity on Kidney Failure and Urinary Incontinence:

Researchers have reported new findings about the effects of excess weight on kidney disease and bladder control. Results from one study that analyzed data from thousands of adults have shown that the more excess weight people carried, the greater their risk for irreversible kidney failure (ESRD)—a serious condition requiring a kidney transplant or life-long dialysis. The risk associated with excess weight existed even among those who did not have diabetes or high blood pressure at the beginning of the study; both of these conditions are also known risk factors for kidney disease. One possible explanation for these findings is that those who carried more excess weight may have subsequently developed diabetes or high blood pressure, which in turn led to kidney failure. Alternatively, excess weight may also lead to kidney failure through other mechanisms. In another study, researchers found that losing a modest amount of weight, through lifestyle changes, reduces urinary incontinence in women who are overweight or obese and have pre-diabetes, a condition in which blood glucose levels are higher than normal but not yet at the point of full-blown diabetes. For this study, researchers analyzed data from the Diabetes Prevention Program (DPP) clinical trial. A major finding of the DPP, reported previously, was that people at high risk for type 2 diabetes can substantially reduce their risk for disease onset through modest weight loss, achieved through a lifestyle intervention to reduce dietary fat and calories coupled with moderately increased physical activity, such as walking. After further analysis, scientists reported this past year that the DPP's lifestyle intervention also reduced episodes of incontinence. These studies underscore the importance of obesity prevention and treatment efforts for kidney and urologic health.

Hsu CY, McCulloch CE, Iribarren C, Darbinian J, and Go AS: Body mass index and risk for end-stage renal disease. Ann Intern Med 144: 21-28, 2006.

Brown JS, Wing R, Barrett-Connor E, Nyberg LM, Kusek JW, Orchard TJ, Ma Y, Vittinghoff E, and Kanaya AM: Lifestyle intervention is associated with lower prevalence of urinary incontinence: the Diabetes Prevention Program. Diabetes Care 29: 385-390, 2006.

ADVANCES IN POLYCYSTIC KIDNEY DISEASE

Polycystic kidney disease (PKD) is an inherited disease characterized by fluid-filled cysts in the kidneys. These cysts, ranging in size from a pinhead to a grapefruit, over time can destroy functioning kidney tissue. This destructive process may result in irreversible kidney failure. There are two forms of inherited

PKD. Autosomal dominant PKD (ADPKD) is one of the most common genetic disorders and seems to affect people regardless of sex or ethnic origin. Autosomal recessive PKD is relatively rare and often causes significant mortality in the first month of life.

The NIDDK supported a clinical study, the Consortium for Radiologic Imaging Studies of PKD (CRISP), to test whether magnetic resonance imaging (MRI) of kidney and cyst volumes is a reliable early marker for monitoring disease progression. CRISP investigators used innovative imaging techniques and analyses to follow disease progression in 241 PKD patients over three years. Several important insights from this study are highlighted below.

Assessing Renal Function in Polycystic Kidney Disease: A new method using magnetic resonance imaging accurately tracks structural changes and likely enables an earlier prediction of functional changes than is possible with standard blood and urine tests in people with ADPKD. The CRISP study found that the cysts grew at a continuous, steady rate specific to each patient and that this enlargement was associated with a decline in kidney function. The CRISP study results suggest that changes in cyst and overall kidney size over time may be a reliable method of monitoring disease progression. With these new insights, researchers may be able to study agents that act earlier in the disease process, before massive enlargement of the kidneys has occurred, and thus find ways to prevent the progression of PKD patients to end-stage renal disease.

The CRISP study also found that high blood pressure, increased kidney volume, and increased cyst volume were all associated with a decline in kidney function in patients with ADPKD. In comparing various methods of estimating changes in kidney function over time, the investigators directly measured glomerular filtration rate—a measure of kidney function—using an exogenous molecule as a marker. This approach produced measurements that had the strongest association with predictors of kidney function decline.

Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King BF, Jr., Wetzel LH, Baumgarten DA, Kenney PJ, Harris PC, Klahr S, Bennett WM, Hirschman GN, Meyers CM, Zhang X, Zhu F, and Miller JP: Volume progression in polycystic kidney disease. N Engl J Med 354: 2122-2130, 2006.

Rule AD, Torres VE, Chapman AB, Grantham JJ, Guay-Woodford LM, Bae KT, Klahr S, Bennett WM, Meyers CM, Thompson PA, and Miller JP: Comparison of methods for determining renal function decline in early autosomal dominant polycystic kidney disease: the Consortium of Radiologic Imaging Studies of Polycystic Kidney Disease cohort. J Am Soc Nephrol 17: 854-62, 2006.

Linking Genetics to Disease Progression in Autosomal Dominant Polycystic Kidney Disease: Previous research showed that two mutated genes, either *PKD1* or *PKD2*, are responsible for most cases of the major form of ADPKD. However, the respective roles of these genes in disease progression, as indicated by ultrasound analysis, have remained unclear. The CRISP investigators, using a more sensitive MRI method, reported that patients with the *PKD1* gene have more cysts and significantly larger kidneys than those with the *PKD2* gene. Data from the CRISP study suggest that this difference results from earlier development of cysts, not from a faster growth of cysts, in patients with *PKD1* mutations. These clinically important results will inform the development of targeted therapies for patients with the most prevalent form of this disease.

Harris PC, Bae KT, Rossetti S, Torres VE, Grantham JJ, Chapman AB, Guay-Woodford LM, King BF, Wetzel LH, Baumgarten DA, Kenney PJ, Consugar M, Klahr S, Bennett WM, Meyers CM, Zhang QJ, Thompson PA, Zhu F, and Miller JP: Cyst number but not the rate of cystic growth is associated with the mutated gene in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 17: 3013-3019, 2006.

UNDERSTANDING THE DEVELOPMENT OF RED BLOOD CELLS

An iron transporter has been found to play an important role in the development of red blood cells and could have significant implications in the treatment of various anemias. Working with zebrafish as a model organism, researchers found that mutant fish with severe anemia were unable to produce red blood cells and had mutations in a specific gene (*mitoferrin,* or *mfrn*). This gene encodes a protein that imports iron into a specialized compartment within developing red blood cells where the molecule heme is synthesized. Heme is the iron-containing component of the molecule hemoglobin, which delivers oxygen in the blood to the tissues of the body and carries away carbon dioxide. The mutations prevented the protein from transporting iron into this compartment and impaired the synthesis of heme—thereby inhibiting the maturation of zebrafish red blood cells. This resulted in severe anemia, which was usually fatal.

Red blood cells derived from mouse embryonic stem cells missing this same gene, and hence the iron transporter, showed a similar failure to develop into mature red blood cells. Furthermore, the gene and its encoded protein appear to be functionally conserved across species; for example, introduction of a normal mouse *mfrn* "rescued" the mutant zebrafish, restoring their ability to produce red blood cells. A corresponding gene has been found in humans, and it is possible that mutations in it may play a role in some congenital forms of anemia in people. The discovery of this gene and its cognate protein provides an important tool for researchers studying iron metabolism and red blood cell development, as well as a potential future therapeutic target.

Shaw GC, Cope JJ, Li L, Corson K, Hersey C, Ackermann GE, Gwynn B, Lambert AJ, Wingert RA, Traver D, Trede NS, Barut BA, Zhou Y, Minet E, Donovan A, Brownlie A, Balzan R, Weiss MJ, Peters LL, Kaplan J, Zon LI, and Paw BH: Mitoferrin is essential for erythroid iron assimilation. Nature *440: 96-100, 2006.*

National Kidney Disease Education Program (NKDEP)

An estimated 10 to 20 million Americans currently suffer from chronic kidney disease (CKD) and, according to the NIDDK-supported United States Renal Data System (USRDS), more than 330,000 patients are on dialysis. Patients with CKD are at increased risk for kidney failure. It is estimated that treating the number of people with kidney failure, also called end-stage renal disease (ESRD), through dialysis or kidney transplantation now costs the U.S. health care system more than $30 billion every year. ESRD is an enormous public health problem that disproportionately affects minority populations.

To help address these issues, the NIDDK supports the NKDEP. This educational program seeks to raise awareness of the seriousness of kidney disease, the importance of testing those at high risk—those with diabetes, high blood pressure, cardiovascular disease, or a family history of kidney disease—and the availability of treatment to prevent or slow kidney failure. The progression from CKD to kidney failure can be prevented or delayed if it is detected and treated early enough. The NKDEP underscores that effective treatments and management strategies for kidney disease exist, yet are being underutilized.

The Program uses several strategies to help achieve its goals. Toward this end, it is implementing public education and awareness initiatives; creating tools and programs for health care providers who play a role in diagnosing and treating CKD and its complications; and spearheading systemic change to improve the accuracy and automatic reporting of estimated glomerular filtration rate (GFR), a measure of kidney function.

Examples of current and recent activities of the NKDEP include:

- *Outreach to People with Diabetes and High Blood Pressure:* In addition to working with specific racial and ethnic populations, the NKDEP is a direct resource to those at risk for CKD due to the two main risk factors—diabetes and high blood pressure. The NKDEP has developed a new, easy-to-read brochure entitled, "Make the Kidney Connection." This brochure encourages people with diabetes and high blood pressure to talk to their health care providers and get tested. Because many people with these conditions are not aware of their risk for kidney disease, and therefore would not think materials on kidney disease relate to them, this brochure focuses on diabetes and high blood pressure to attract their attention. The brochure, suitable for a diverse population, was reviewed by an expert panel and audience-tested through focus groups and in a real-world setting.

- *Outreach to Family Members of Dialysis Patients:* Several years ago, the NKDEP developed materials entitled, "Help Your Family Prevent Kidney Failure," to encourage dialysis patients to talk to family members about their risk of developing kidney disease. To optimize distribution of these materials, "The Dialysis Center Working Group" was convened to advise the NKDEP regarding how best to interact with dialysis centers. The working group meeting prompted a joint mailing with the Forum of ESRD Networks to dialysis centers to inform dialysis patients about NKDEP materials and other relevant materials from the

NIDDK's National Kidney and Urologic Diseases Information Clearinghouse.

- *Creatinine Standardization Program:* The NKDEP's Laboratory Working Group is leading an effort to reduce inter-laboratory variation in creatinine assay calibration, which is critical to improving the accuracy of estimates of glomerular filtration rate (eGFR)—a key measure of kidney function. The new recommendations on measuring serum creatinine provide an opportunity to detect CKD earlier. Launched in 2006, the program encourages *in vitro* diagnostic manufacturers to recalibrate serum creatinine methods to those that are traceable to "perfect" standards in measurement procedures and support customer laboratories in the transition from using current methods to those that are standardized. The Laboratory Working Group's recommendations for creatinine standardization were published in the January 2006 issue of *Clinical Chemistry*.

- *2006 Family Reunion Initiative Kicks Off:* The NKDEP has kicked off the second year of its African-American Family Reunion Initiative. The goal of the initiative is to encourage African-American families to discuss the connection among diabetes, high blood pressure, and kidney disease at reunions and other family gatherings. This year, the NKDEP has expanded the Kidney Connection Guide—to include additional tips for planners and fact sheets on diabetes and high blood pressure.

- *New Spanish-Language Initiative:* The NKDEP launched a new Spanish-language initiative to raise awareness about risk factors for CKD among Hispanic Americans. The initiative includes a website and brochure that highlight the connection between kidney disease and its primary risk factors—diabetes and hypertension. Hispanics are disproportionately affected by diabetes and hypertension, and are nearly twice as likely to develop kidney failure as non-Hispanic whites. The website and brochure provide science-based information on the risk factors for kidney disease, the basic principles of kidney function, as well as the importance of early testing. The materials stress that someone can have kidney disease without knowing it. The materials also stress the availability of medications that can prevent or slow the disease progression. Both resources offer additional Spanish-language resources on diabetes, hypertension, and kidney disease. The new materials were developed in collaboration with kidney disease experts and dialogue in Spanish with community-based organizations serving the Hispanic community. To view the NKDEP Spanish-language website, and to download or order the brochure, visit *www.nkdep.nih.gov/espanol*

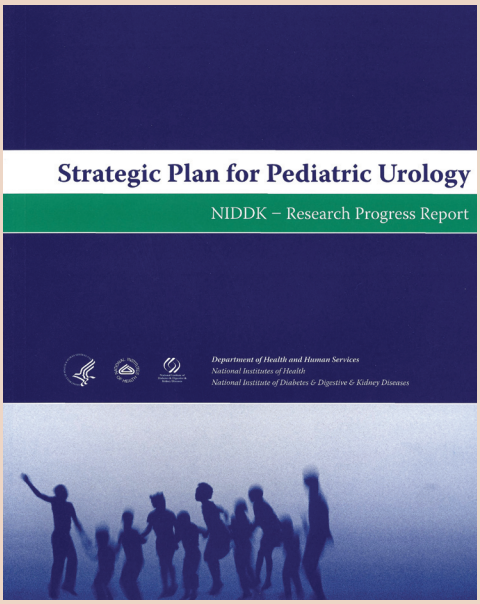
Through continued educational efforts, the NKDEP contributes to helping primary care providers better assess, treat, and educate patients about CKD; to improving the use of diagnostic tools by health care practitioners; and to coordinating Federal efforts in this area.

More information about the NKDEP can be found at *http://www.nkdep.nih.gov*

A Strategic Plan for Research in Pediatric Urology

The Strategic Plan for Pediatric Urology, NIDDK—Research Progress Report, published in February 2006, was developed under the Institute's auspices with the contributions of external experts in urology. The Plan's Executive Summary conveys the many challenges intrinsic to pediatric urological diseases, for example, the need to discriminate between children at risk for severe long-term complications requiring intervention and the larger group who are not; the complexity and variety of the congenital anomalies; and the need for multicenter clinical trials to study the relative infrequency of many conditions. In addition, the Plan addresses topics such as the health impact of pediatric urological diseases, the major clinical needs in pediatric urology; the clinical presentation and treatment of these diseases; and basic, clinical, and translational research priorities.

An example of one of the diseases highlighted in the Plan is vesicoureteral reflux (VUR), a disease of the lower urinary tract. VUR results from a developmental defect in which abnormal insertion of the ureter into the bladder causes retrograde flow of urine into the ureter and the upper urinary tract. Consequently, patients are at an increased risk for urinary tract infections leading to kidney damage or scarring. In follow-up to recommendations in the Plan, the NIDDK is about to launch the Clinical Study of Vesicoureteral Reflux in Children, a trial which aims to recruit a group of approximately 600 affected children to determine which ones are likely to benefit from long-term antibiotics and which ones are at the highest risk for scarring of the kidneys and progression to kidney failure.



The *Strategic Plan for Pediatric Urology, NIDDK—Research Progress Report*, published in February 2006, identifies priorities for research on urological conditions that affect children. The report was developed by the NIDDK with input from external experts in the field. It can be accessed on the NIDDK website at: *http://www.niddk.nih.gov/federal/planning/Pediatric-Urology/*

PATIENT PROFILE

Andrea Arnold

Coping with Chronic Kidney Disease at Age 13

It's 7:15 on a Wednesday morning. While her friends are heading off to school, 13-year-old Andrea Arnold's grandmother has just dropped her off at the outpatient dialysis unit at Children's Hospital. By the time Andrea settles in, is weighed, has her temperature and blood pressure checked and her heart and lungs assessed by the unit's staff, it's around 8:00 a.m.

As she makes herself comfortable in a medically designed reclining chair, one of the staff members inserts two needles into the vascular access on Andrea's upper right thigh. One needle carries Andrea's blood to the dialyzer, a medical device that will remove the harmful waste products that accumulate in her blood because doctors had to remove her kidneys; the other needle returns the cleansed blood to her body. Andrea winces a bit when the needles are inserted. It's one of the most unpleasant parts of hemodialysis. For the next 3 hours and 15 minutes Andrea will sit back in the recliner while the dialysis machine rhythmically whirrs and beeps, pumping and cleansing her blood and removing excess fluid from her body to keep her alive. This routine takes place 3 days a week.

Cora Dixon tutors Andrea while she's being dialyzed. "Andrea's a good student and should be an attorney," says Ms. Dixon, who adds that Andrea asks very challenging questions, especially about her health. Unfortunately, many of the answers would be daunting for an adult, let alone a 13-year-old.

Andrea Arnold

For the next 3 hours and 15 minutes Andrea will sit back in the recliner while the dialysis machine rhythmically whirrs and beeps, pumping and cleansing her blood and removing fluid from her body to keep her alive.

CHRONIC KIDNEY DISEASE

Andrea has reflux nephropathy, which occurs when a faulty one-way valve-like system allows urine to flow back from the bladder up to the kidneys. Because the pressure in the bladder is generally higher than in the kidneys, the reflux of urine exposes the kidneys to unusually high pressure. Over time, this increased pressure will damage the kidneys and cause scarring, which could lead to chronic kidney failure and

PATIENT PROFILE

end-stage renal (kidney) disease, as it did with Andrea. Andrea was diagnosed with urinary reflux to the kidney when she was 6 months old, acute kidney disease at the age of 3 years old. She progressed to chronic kidney disease at the age of 9. At age 12, she had both of her kidneys removed. Reflux nephropathy can run in families. Andrea has a 14-year-old brother, André, but fortunately, he shows no signs of the disease.

About four out of 1,000 children have reflux, but show no symptoms. Up to 50 percent of infants and children with urinary tract infections have reflux. It is estimated that reflux nephropathy may cause as many as 20 percent of the cases of renal failure in children and young adults. Young girls are especially prone to infections because their urethra, which is the tube leading from the bladder to outside the body, is relatively short compared to that of boys. This shortness makes it easier for germs from outside the body to make their way to the bladder.

Andrea also had a condition called chronic pyelonephritis. Pyelonephritis is infection and inflammation of the kidneys. The combination of reflux and bladder infections exposes the kidneys to the possibility of pyelonephritis. *Chronic* pyelonephritis is a long-standing infection that does not clear and can, over the years, increasingly damage the kidneys. It, too, can cause end-stage renal disease. In Andrea's case, it necessitated the removal of both her kidneys.

To compound matters, Andrea has an enlarged heart as a result of the hypertension from her kidney disease. Although she takes several medications, she's allergic to one of the antibiotics commonly used in the treatment of reflux. She also has asthma, further complicating her treatment.

LIVING WITH CHRONIC KIDNEY DISEASE

In many ways, Andrea's entire childhood has been defined by her disease. At just 6 weeks old she was hospitalized with a bladder infection. Three months later, young Andrea was back in the hospital with another bladder infection. By age 6 months Andrea was diagnosed with reflux and once again hospitalized. "It just continued to get progressively worse," says Andrea's mother, Patrice Arnold.

A year after being diagnosed, Andrea had her ureters, which carry urine from the kidneys to the bladder, surgically reimplanted into her bladder to help stop the reflux and to diminish the frequency and severity of her kidney infections. In all, Andrea has undergone seven surgeries related to her kidney disease. One required her to wear an appliance (urostomy bag) for many years, until her kidneys were removed. As a result of her kidney disease, Andrea's body has difficulty maintaining an appropriate balance of the minerals calcium and phosphorus, and her bones are weak.

According to Andrea, the worst thing about having this disease is that it has stunted her growth. "I grow slower than most kids my age," says the precocious adolescent. Andrea weighs just under 90 pounds and is four feet, nine inches tall. "I wish I were a bit taller," she says.

Andrea claims that she feels little, if any, pain as a result of her current condition, but her kidneys "hurt a lot" from the time that she was 6 years old until they were removed 6 years later.

Because their blood types match, Andrea's mother is hoping to be able to donate one of her kidneys to her daughter. For now, Andrea must carefully monitor her calcium and phosphorus levels and follow a strict diet, a difficult assignment when you're 13 years old and want to be like every other 13-year-old.

"I'd just like to do more things with people my age," says Andrea, "like eat French fries, chocolate, ice cream, dark sodas (colas), tomatoes, fresh fruit," all of which she is restricted from eating because of their high levels of sodium, phosphorus, or potassium. Andrea also says that she liked to dance "before my bones got too weak." If she were healthier, she'd like to play basketball. "I'd get to run and play with the other kids," she says.

"I'd just like to do more things with people my age," says Andrea, "like eat French fries, chocolate, ice cream, dark sodas (colas), tomatoes, fresh fruit," all of which she is restricted from eating…."

In the meantime, while she waits in hope that she will be able to receive a kidney from her mother, Andrea will remain on hemodialysis 3 days a week, as she has for the past 2 years.

"I do most of my homework when I'm on the machine (dialyzer)," says Andrea. When she's not being tutored, volunteers come in to entertain her and the other kids in the dialysis unit with crafts and painting. "I've made friends with the other children here with kidney disease," says Andrea. "We don't see each other as sick. We're just close friends and we talk about everything." But she quickly adds that she'd rather be home, in school, or at the mall than being dialyzed.

It's nearly 11:30 on this particular Wednesday morning. Amid the quiet bustle of the outpatient dialysis unit, Andrea will once again be weighed, have her temperature and blood pressure taken, and her heart and lungs assessed before she leaves for the day. Today, she says, she feels fine, but there are days when she's a little dizzy or weak after her dialysis. She will be taken home to her great-grandmother and grandmother's house, where Andrea will either finish whatever homework she has left or lie down and take a nap until her mother gets off from work to pick her up later this evening. It's already been a long day for this courageous 13-year-old.

When asked if she has a message for kids her age, Andrea replies without hesitation "that you should never feel sorry for yourself. There's always someone worse off than you."

PATIENT PROFILE

Hope Through Research

The NIDDK supports a range of programs and studies devoted to improving treatment for patients like Andrea and others with progressive kidney disease and permanent kidney failure, including those on hemodialysis.

- The NIDDK—along with several other Institutes at the NIH—has established the Chronic Kidney Disease in Children (CKiD) study to recruit over 500 children with mild to moderately decreased kidney function and follow them for 5 years. Researchers will study risk factors for further decrease in kidney function; closely monitor brain development; examine risk factors for heart disease; and look at the long-term effects of poor growth in this group.

- The NIDDK is about to launch the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) clinical trial. This trial aims to recruit a group of children with vesicoureteral reflux to determine which ones are likely to benefit from long-term antibiotics and which ones are at the highest risk for scarring of the kidneys and progression to kidney failure.

- NIDDK's End-Stage Renal Disease Program promotes research to reduce medical problems from the complications of kidney failure and to improve the effectiveness of dialysis and transplantation.

- The upcoming Hemodialysis Vascular Access Clinical Trials Consortium will conduct a series of clinical trials of drug therapies to reduce the failure and complication rate of vascular access in hemodialysis.

- The U.S. Renal Data System (USRDS) collects, analyzes, and distributes information about the use of dialysis and transplantation to treat kidney failure in the United States. It also helps identify problems and opportunities for more focused special studies of kidney research issues.

STORY OF DISCOVERY

Ironing Out the Anemia of Inflammation

In a feat of scientific serendipity, researchers have now discovered that a molecule first found in a search for antimicrobials lies at the crux of the anemia of inflammation—the second most common form of anemia.

How Various Forms of Anemia Can Result from Low Iron Levels: Anemia is a potentially serious health condition that occurs when the blood suffers a drop in its capacity to deliver oxygen throughout the body. Iron is essential to the body's oxygen-delivery system. Humans need iron to make hemoglobin, the oxygen-carrying molecule in red blood cells. Because it can be dangerous to have too much iron (as well as too little), total body iron is carefully regulated, with most of it being constantly recycled. While small amounts are absorbed daily via the digestive tract, about 10 times more iron is simply retrieved from aged red blood cells and reused. Special cells in the liver and spleen digest red blood cells and release their iron to the blood. A protein called transferrin picks up this iron, along with the dietary iron that has been absorbed via the digestive tract. Transferrin then carries the iron to the bone marrow, where it is used to make new red blood cells. If insufficient iron flows to the bone marrow, however, normal red blood cell production drops and anemia can result. Without treatment, even mild anemia stresses the body, which tries to compensate for reduced oxygen levels by increasing heart rate and respiration. Thus, one important cause of anemia is iron deficiency, the most common cause of anemia, which can be corrected through administration of iron supplements. Another form of anemia, however, is associated with inflammation.

Understanding the Anemia of Inflammation and Chronic Disease: The anemia of inflammation and chronic disease affects people who have infections, chronic inflammatory disorders—such as rheumatoid arthritis—and many chronic disorders, including cancers. It may also occur with acute, critical illnesses. While this form of anemia resolves if the underlying condition resolves and is not usually severe, it can contribute to a poorer prognosis for affected patients. Patients with this form of anemia typically have inadequate red blood cell production, low blood iron (hypoferremia), and low levels of transferrin; they are also resistant to the effects of erythropoietin, the hormone that normally stimulates and regulates red blood cell production. Patients with the anemia of inflammation and chronic disease are usually not iron-deficient. Instead, the iron balance in their bodies has been altered, such that more iron is sequestered in the cells involved in iron recycling and absorption, as well as in liver cells that store iron. This cellular sequestration of iron leaves less available for transport to the bone marrow. Attempts to treat the anemia of inflammation and chronic disease with oral iron supplements typically do not work, even though this form of anemia mimics iron deficiency. Rather than being used for red blood cell formation, the new iron is simply added to the cellular stores. Thus, a major mystery has been why these cells do not relinquish sufficient iron to restore iron flow to normal and thus avert anemia.

For several decades, scientists studied the effect of inflammation and chronic disease on iron metabolism, but these studies were not able to fully explain the iron

STORY OF DISCOVERY

sequestration. Now, a series of fortuitous discoveries by NIH-supported researchers and others has solved part of the puzzle with the discovery of hepcidin.

Role of Hepcidin: Hepcidin was identified 6 years ago in a search for small molecules active in "innate immunity," the body's first-line of defense against invading bacteria, fungi, and other microorganisms. Examining urine and blood samples from humans, researchers found a small, hairpin-shaped molecule structurally similar to antimicrobial molecules in other species. To their surprise, however, the gene encoding the molecule—later named hepcidin—was expressed predominantly in the liver. This finding took an important turn when a research team studying a condition called "iron overload" found that liver production of hepcidin increased in mice given excess iron. A rapid succession of studies in animal models and humans followed. From this research, hepcidin emerged as a fundamental regulator of iron balance that inhibits iron absorption and iron release from tissue stores when iron levels are high, and eases off when iron levels decline.

How does hepcidin contribute to anemia of inflammation and chronic disease? It turns out that hepcidin production is not only stimulated by increased iron levels, but also by inflammation. Researchers studying hepcidin found that if they induced inflammation in mice, liver production of hepcidin quickly rose. At the same time, blood iron levels fell—similar to what is seen in this form of anemia. This inflammatory response was ablated, however, if the mice were hepcidin-deficient, or if they lacked a certain inflammatory molecule, called cytokine IL-6. These findings indicated that, in response to IL-6, hepcidin mediates inflammation-induced drops in plasma iron.

Reinforcing these results in mice, a clinical study showed that IL-6 administration led to a rapid rise in hepcidin levels and drop in plasma iron in people. Concomitantly, research showed that people with anemia of inflammation have elevated levels of hepcidin in their urine—thus confirming that hepcidin has an important role in causing this health condition.

Scientists have also uncovered the way that hepcidin likely causes the drop in plasma iron. Cells handling iron transport have several ways to obtain iron, but only one way to export it, through a so-called "transporter protein" in the cell membrane called "ferroportin." In experiments with cultured cells, hepcidin binds to ferroportin and induces its destruction, thereby preventing iron from exiting cells. This key finding explains why iron accumulates in cells that store iron, but is not released for use by the bone marrow.

Thus, hepcidin-induced sequestration of iron in response to inflammation explains—in whole or in part—how affected patients can be replete with iron but, ironically, cannot use it. Scientists are still grappling with the question of why this state is permitted to continue, given that iron pathways in the body normally try to correct anemia. Indeed, in animal models, other forms of anemia normally decrease hepcidin expression, thus increasing iron flow. Yet, in the anemia of inflammation and chronic disease, the interaction between IL-6 and hepcidin overrides other body signals and causes and maintains anemia.

Therapeutic Possibilities: Consistent with hepcidin's role as a regulator of iron balance, the dysfunction or dysregulation of this molecule is implicated in a number of iron overload disorders. Recent studies suggest that pathways important in iron overload may

provide a promising route for preempting hepcidin's role in anemia of inflammation. Special attention has focused on one form of inherited iron overload, "juvenile hemochromatosis." In humans, mutations in the gene encoding a protein called hemojuvelin result in this severe, early-onset iron overload. A recent study showed that mice genetically engineered to lack hemojuvelin not only exhibited iron overload, but also had reduced hepcidin levels and increased ferroportin. These results showed that hemojuvelin is important in regulating the hepcidin pathway. Subsequently, scientists determined that there are two forms of the hemojuvelin protein—a longer, cell-associated form, and a shorter, "soluble" form found in blood. While the full-length hemojuvelin protein appears to positively regulate hepcidin gene expression, the soluble form exerts a negative effect on hepcidin levels and, most importantly, inhibits hepcidin stimulation by the cytokine IL-6. Thus, researchers are exploring the possibility that soluble hemojuvelin may provide a therapeutic approach with which to modulate abnormal hepcidin levels in the anemia of inflammation and thereby to correct the anemia.

This rapid progress in identifying hepcidin and discovering its role at the intersection of inflammation and iron metabolism has been critical to progress in understanding the anemia of inflammation and chronic disease. While it has yet to be determined whether excess hepcidin is sufficient to cause this form of anemia, its key role in the underlying biologic process has been firmly established.

While much has been learned, an intriguing research question remains: why would the body choose to exacerbate illness by causing anemia when a patient is sick? Iron is not just essential for human life; it is also used by invading microbes and rapidly growing tumor cells. Researchers speculate that this "iron sequestration response" developed during evolution because it favored survival from infections, for when the body "hides" iron and prevents its further uptake via the digestive tract, it establishes a defense mechanism that hinders the growth of infectious organisms. However, this defense mechanism incurs a cost by causing anemia. Moreover, it is misdirected in patients with chronic inflammatory conditions (such as rheumatoid arthritis), and it is inappropriately active in older persons in the absence of any infection or malignancy. Researchers will need to consider the potential harm or benefit of changing iron availability in different conditions associated with the anemia of inflammation and chronic disease as new discoveries about hepcidin are translated into new therapies for this common form of anemia.

SCIENTIFIC PRESENTATION

Tipping Iron Balance

Dr. Nancy Andrews

Dr. Nancy Andrews is a leading researcher in the field of iron biology. Her research group focuses on iron transport pathways involved in systemic iron homeostasis, and the elucidation of molecular mechanisms underlying diseases of iron uptake and deficiency. Dr. Andrews is the George R. Minot Professor of Pediatrics and the Dean for Basic Sciences and Graduate Studies at Harvard Medical School, a Senior Associate at Children's Hospital Boston and a Distinguished Physician of the Dana-Farber Cancer Institute. The following are highlights based on a scientific presentation Dr. Andrews gave at a meeting of the Institute's National Advisory Council in September 2006.

Dr. Andrews focused her presentation on genes and cellular pathways that she and her collaborators have discovered are directly involved in inherited diseases of toxic iron overload, known collectively as "hereditary hemochromatosis." She then turned her attention to her group's recent search for modifier genes that affect these primary pathways—and, hence, can also tip overall iron balance. Through a wealth of fundamental studies, she and her research team are finding and fitting together various pieces of the puzzle of iron homeostasis that will help point the way to new approaches to treating iron overload disorders.

IRON HOMEOSTASIS

Dr. Andrews began by explaining iron homeostasis, or the regulation of iron movement and metabolism that leads to stable iron levels in the body. Iron is an essential element absorbed from the diet. Absorption is normally very tightly regulated, because there is no specialized mechanism for excreting iron, which can become toxic in high amounts. Iron is only lost from the body through bleeding and through the shedding of skin cells and cells lining part of the digestive tract. Only a small amount of iron (1 to 2 milligrams) enters the body every day, to balance or only slightly exceed these small daily losses.

Some of the body's iron circulates in a form bound to the plasma protein, transferrin. This iron is primarily delivered to the bone marrow, where it is incorporated into hemoglobin in developing red blood cells. About two-thirds of the iron in a healthy individual is found in red blood cells and their precursors. Over time, old or damaged red cells are engulfed by cells called tissue macrophages, which break them down and "recycle" their iron, returning it to transferrin for reuse. Iron is also used by all other cells and tissues in the body, in very small amounts. The remaining body iron is generally deposited in the liver. Normally, total iron content in the human body is about 2 to 4 grams.

HEREDITARY HEMOCHROMATOSIS

Hereditary hemochromatosis is a disease that develops because of increased dietary iron absorption, and it is characterized by increased serum iron levels. Excess iron is deposited in a variety of tissues, where it catalyzes the formation of toxic oxygen species (free radicals) and in that way causes tissue damage. The primary target organs for deposition of excess iron include the liver, where iron loading results in fibrosis, cirrhosis, and a markedly increased predis-

position to hepatocellular carcinoma; the heart, where it is associated with cardiomyopathy and arrhythmias; and in endocrine tissues such as the pancreas, where it disrupts normal function and may impair insulin secretion and cause diabetes.

The small intestine is the gatekeeper for the absorption or exclusion of dietary iron. To enter the circulation, dietary iron must be picked up on the apical (top) side of cells lining the small intestine, and then be released through their "feet," or the basolateral side. Over-absorption of iron could thus result from excess iron being picked up on the apical side (and then dumped out the basolateral side), or from dysregulated iron release on the basolateral side. To understand iron transport pathways in the absorptive cells lining the small intestine, Dr. Andrews' research team took advantage of the knowledge that vertebrates are very similar in how they deal with iron. Thus, by studying rodents and other animals with heritable iron transport defects, they could then use powerful genetic techniques to identify the genes affected, and hence the molecules responsible.

One iron transporter discovered through these studies was ferroportin. Iron transport defects lead not only to iron overload, but also to iron deficiency, and hence, anemia. A fellow scientist studying severe anemia in a zebrafish mutant animal model strain (*"Weissherbst"*) identified a mutant gene that was implicated in basolateral iron transport. The gene encoded ferroportin. A collaborative research effort ensued and led to the extensive characterization of mouse ferroportin in the Andrews lab. Ferroportin is present in the cell membrane of intestinal cells and macrophages, and is the only known "iron exporter" in cells. Because of its likely role in human hemochromatosis, Dr. Andrews' lab pursued studies of its regulation.

While these studies were under way, the serendipitous discovery of "hepcidin" by other researchers yielded another key piece of the puzzle of how iron homeostasis is controlled. Hepcidin is a small protein that controls serum iron concentration by regulating export of iron recycled from old red cells to the serum, and also by controlling intestinal iron absorption. Hepcidin is produced almost exclusively by the liver, in varying amounts that depend on iron needs.

With the key observation that inherited iron overload is associated with low levels of hepcidin, studies of ferroportin and hepcidin became linked. Research soon revealed that hepcidin inhibits ferroportin activity by binding to it and causing its degradation. These findings led to an updated model for iron homeostasis. In this model, ferroportin activity is normally regulated by hepcidin, such that some iron stays in the intestinal cells or in the macrophages, and some is released. In hemochromatosis, however, low hepcidin levels lead to increased ferroportin activity—i.e., increased iron export—and, in turn, to the increased serum iron that causes deposition of iron in the liver, heart, and elsewhere. This model provided the springboard to the next steps in studying iron overload—determining where genes implicated in different forms of hemochromatosis fit into the iron puzzle.

COMPLEXES IN IRON REGULATION

Dr. Andrews explained that there are two types of inherited hemochromatosis. Adult onset hemochromatosis is relatively mild and can be

SCIENTIFIC PRESENTATION

caused by mutations in the ferroportin gene, a gene called *HFE*, or a gene called *TFR2*. Juvenile, or early-onset, hemochromatosis is more severe and can be caused by mutations in the hepcidin gene, or in the most recently discovered hemochromatosis disease gene, *HJV*, which encodes the hemojuvelin protein.

Studies in mouse models, as well as examination of patients, soon indicated that these hemochromatosis-inducing mutations actually fall into three functional "classes": mutations in the ferroportin gene, which change the function of this iron exporter; mutations in the hepcidin gene, which directly affect its regulation of ferroportin; and mutations in the other genes (*HFE*, *TFR2*, and *HJV*), which lead to reduced hepcidin levels—indicating that these three genes are involved in regulating hepcidin. *HJV* mutations exert the most severe effects on hepcidin levels, while *HFE* and *TFR2* mutations have milder effects, which suggests that they act to "fine tune" hepcidin production. Thus, an important goal for the Andrews lab has been to work out how the proteins encoded by these three genes regulate hepcidin—most importantly, the role of hemojuvelin.

A break came in deciphering hemojuvelin's role when studies by another NIDDK-supported investigator suggested that hemojuvelin and similar proteins might act as co-receptors for bone morphogenetic proteins, or BMPs. This was exciting because BMP proteins are involved in regulating expression of a wide variety of genes, including genes affecting growth, development, and bone. BMPs interact with specific receptors on the cell surface to stimulate a signaling cascade inside the cell that ends with changes in gene expression. "Co-receptors" can help direct, refine, or amplify BMP-induced changes in gene expression in different cell types by interacting with a BMP and/or its receptor.

A series of collaborative studies in mouse models and in cultured cells indicated that hemojuvelin indeed acts as a co-receptor in a BMP pathway. Through a set of elegant experiments, Dr. Andrews and her colleagues showed that hemojuvelin forms a complex with BMP and a BMP receptor to initiate a signaling cascade that leads to hepcidin expression in liver cells. This key finding was followed by studies suggesting that the HFE protein takes the same molecular journey—that HFE joins the hemojuvelin-BMP-BMP receptor complex when iron levels are high and it is "freed" from its association with another iron regulatory protein (TFR1). Moreover, biochemical experiments showed that the third putative hepcidin regulator, TFR2 protein, interacts with HFE and also becomes part of the complex when iron levels are high. TFR2 may also play an important role in keeping the entire complex stable. Thus, at least these three proteins—and possibly more—appear to be involved in a large regulatory complex that helps modulate BMP signaling for hepcidin production.

So why make the signaling complex so complicated? Dr. Andrews proposed that this assemblage allows for a rheostat-like regulation of hepcidin expression. In her model, the absence of the hemochromatosis-associated proteins means that BMP-induced hepcidin levels are minimal. Adding just hemojuvelin back to the complex restores much of its activity and provides a very large induction of hepcidin expression. However, in order to have full production in the face of increasing iron levels, HFE and TFR2 may be required.

MODIFIER GENES THAT AFFECT IRON BALANCE—ALTERING THE IRON SET POINT

In the most common form of hemochromatosis, caused by *HFE* mutations, there is great variability in how severely the disease affects human patients. In contrast, genetically identical mice with *HFE* hemochromatosis do not show such variability. This observation suggests that there are modifier genes in human populations that affect the clinical expression of this disease. Such genes modify the so-called iron set point, and are important to understanding both iron pathways and the course of iron overload disease in individuals.

To look for modifier genes, Dr. Andrews' research team approximated the human situation by comparing the iron levels of different mouse strains—i.e., of mice that are not genetically identical. The researchers could later use powerful genetic tools to isolate the relevant differences. Upon examining iron stores in the liver and spleen (the primary site of red blood cell iron recycling) in nine different mouse strains, the team found substantial variation. In particular, two of the strains exhibited very large differences in iron content. The researchers then performed a genetic mapping experiment: "low iron" and "high iron" mice were bred together. The offspring were then bred with each other, creating a so-called "F2 generation." The purpose of this breeding was to generate mice whose chromosomes were patchworks of chromosomes from the "pure" strains—permitting researchers to more readily "map" characteristics, such as differences in body iron levels, to particular chromosomes.

The "patchwork" F2s exhibited a very wide range of liver and spleen iron content. This indicated that multiple genes were likely involved in the iron differences. Turning the data from those F2 mice into chromosomal positions, they found that liver iron characteristics were associated with four different chromosomes. In contrast, most of the difference in spleen iron between the two strains was associated with mouse chromosome 9.

Focusing on chromosome 9 and spleen iron content, Dr. Andrews explained how her research team used molecular tools and more genetic mapping methods to gain further insights. Going back to the original mouse strains, they introduced smaller and smaller pieces of chromosome 9 from the "high iron" mouse strain into the genome of the "low iron" strain. By performing these manipulations and then looking at the effect on spleen iron content in the resulting mice, they were able to narrow down the candidate segment of chromosome 9 from a region encompassing hundreds of candidate genes to a region encompassing just a few. A single candidate gene, "gene B," eventually emerged from this study. By analyzing the DNA sequence of gene B from the two mouse strains, they found that a unique genetic variation could explain why the "low iron" mice are so different from other strains.

Using molecular tools, the team studied the protein product of gene B in the "low iron" and "high iron" mice. They initially detected this protein, "protein B," inside iron-recycling macrophages from the mouse spleen. However, the amount of protein B didn't appear to differ between "high-" and "low iron" mice. Thus, the team wondered whether, instead, protein B influences proteins involved in iron accumulation. The iron exporter ferroportin was a good candidate. What they found when they compared spleen ferroportin levels between the two mouse strains was that spleen macrophages from "low iron" mice had more

ferroportin on their surface (and hence more exit points for iron) than those from "high iron" mice—consistent with the reduced accumulation of iron in the spleens of "low iron" mice. While the exact mechanism has yet to be worked out, these initial studies suggest that protein B is involved in some way in membrane trafficking of ferroportin, independent of hepcidin.

SUMMARY AND FUTURE STUDIES

Hereditary hemochromatosis is a genetic iron overload disease that can be caused by different genes and ranges in severity. Mutations in the hepcidin gene cause hemochromatosis because no functional hepcidin protein is produced. Mutations in ferroportin can, in some cases, cause hemochromatosis because the mutant ferroportin is no longer regulated appropriately by hepcidin. Mutations in the other three hemochromatosis-associated genes are thought to cause hemochromatosis by inactivating components of a BMP signaling complex involved in inducing hepcidin expression.

Within *HFE* hemochromatosis, there is variability in disease severity among individuals. The Andrews lab is searching for genes that might modify hemochromatosis severity in mice as a way to discover why the severity of hemochromatosis varies in people. Gene B and its protein product are likely candidate hemochromatosis disease modifiers.

Future studies will focus in detail on what the function of protein B is, and whether variants in gene B actually influence hemochromatosis in mouse models—and, if so, whether there are disease-relevant gene B variants in human patients. Dr. Andrews briefly described exciting studies being pursued by young investigators in her lab. These focus on candidate modifier genes for liver iron content, and candidate serum proteins that modify hepcidin expression. She closed by noting that, as a principal investigator and in her position as the Dean of Basic Sciences and Graduate Studies, her greatest concern is keeping extremely talented young investigators involved in science.