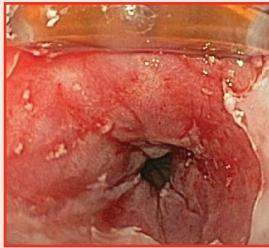


ADVANCES IN ADULT AND PEDIATRIC GASTROENTEROLOGY AND GI SURGERY

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College

JANUARY 2014

1 A Multipronged Attack on Barrett's Esophagus



Endoscopic radiofrequency ablation of Barrett's esophagus

A Multipronged Attack on Barrett's Esophagus

- How does Barrett's esophagus develop in patients?
- Which patients with Barrett's esophagus are at risk for developing cancer?
- How can we prevent the progression of Barrett's to cancer?

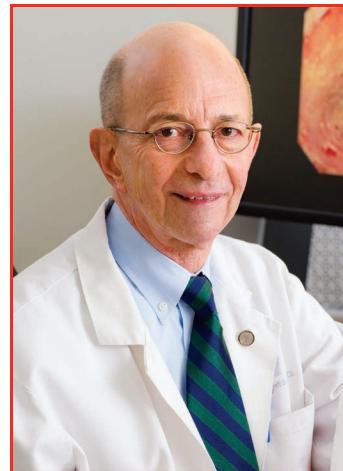
These three questions are at the heart of the research and clinical efforts of Julian A. Abrams, MD, MS, Charles J. Lightdale, MD, and their colleagues in the Division of Digestive and Liver Diseases at NewYork-Presbyterian/Columbia University Medical Center. And the answers can't come soon enough.

"Esophageal adenocarcinoma – the cancer that develops from Barrett's – is the fastest accelerating cancer in the United States today," says Dr. Lightdale, the Division's Director of Clinical Research. "It's also a very lethal cancer. We're determined to try to prevent it or at least catch it at a very early, curable stage."

In the four decades that Dr. Lightdale has been studying and caring for patients with Barrett's esophagus, he has seen the incidence of esophageal cancer rise 600 percent. Affecting one to two percent of the population, Barrett's esophagus most commonly appears in Caucasian men over the age of 50. It is associated with risk factors that include smoking, obesity, and, most importantly, a history of acid reflux. About two percent of those with Barrett's will go on to develop esophageal adenocarcinoma, and of particular interest is that 85 percent of these esophageal cancers are also in Caucasian men.

Why Barrett's serves as a precursor to cancer in a small percentage of people is a big unknown, says Dr. Abrams. "This is one of the major areas that we're researching. We're trying to figure out who is more likely

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Dr. Charles J. Lightdale

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Inflammatory Bowel Disease: Approaching Therapeutics from Multiple Perspectives

When the Jill Roberts Center for Inflammatory Bowel Disease was established in 2006 at NewYork-Presbyterian/Weill Cornell Medical Center under the leadership of Ellen J. Scherl, MD, the Center's physicians had 700 patient visits. Just seven years later, that number has grown to more than 10,000. As the Center's patient population continued to increase so did the number of its faculty members and the range of research to better understand its causes and clinical trials to effect better treatments. In fact, at NewYork-Presbyterian/Weill Cornell, there are now five gastroenterologists devoted to the Center's patient care and research efforts, and some 30 ongoing research projects and clinical trials in IBD, including those specific to its most common forms – Crohn's disease and ulcerative colitis.

According to Dr. Scherl, the combination of an environmental change and alteration in the gut microbiome in a genetically susceptible host can result in uncontrolled inflammation and unregulated immune response. "Understanding the interplay among genetic susceptibility, the microbiome, the environment, and the immune system is essential for developing optimal therapeutic strategies for IBD," says Dr. Scherl, who, in collaboration with Kenneth W. Simpson, PhD, a microbiologist at Cornell University's College of Veterinary Medicine, identified a novel *E. coli* bacteria associated with Crohn's disease.

Building on research in Crohn's disease that demonstrated global imbalances of the intestinal microbiome (dysbiosis) characterized by a

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predominance of aggressive bacterial species, Drs. Scherl, Simpson, and their colleagues examined the dynamics of the relationship between inflammation and changes in the ileal microbiome in murine models of ileitis. Using environmental triggers and pathomechanisms relevant to Crohn's disease, their research provided important information for developing effective therapies by establishing the following:

- acute ileitis induces dysbiosis and proliferation of mucosally invasive E. coli, irrespective of trigger and genotype
- dysbiosis induced by toxoplasma gondii is significantly muted and bacterial invasion prevented when the inflammatory response is limited by the deletion of CCR2 – a pro-inflammatory chemokine receptor – making it a potential target for therapeutic intervention

"While the specific factors related to inflammation that induce dysbiosis still need to be clarified, we speculate that inflammation-related perturbations in the microenvironment underly this phenomenon," says Dr. Scherl. "It also seems plausible that genetic susceptibility may influence the ability of an individual to resolve the self-perpetuating cycle of dysbiosis and inflammation generated by an acute insult. One of our goals is to identify new inflammatory targets for therapeutic development.

"The overarching, organizing principle is that we're moving from biologics to cellular regeneration and stem cells, and now to an infectious origin," continues Dr. Scherl. "The reason we're talking about immune therapy – whether it's biologic or stem cell – is that bacteria or something in the environment of the gut stimulates an upregulated, uncontrolled immune-mediated inflammation."

So what is it about the environment that results in this increase of uncontrolled inflammation?

To help answer this question, Dr. Scherl and her research team are now conducting a study in ulcerative colitis looking at the whipworm *Trichuris suis*. "Trichuris suis acts as a decoy so that your immune system attacks the worm and leaves your gut mucosal alone."

Physician-scientist Randy S. Longman, MD, PhD, is also exploring the question in his laboratory work. Dr. Longman recently joined the Jill Roberts Center for Inflammatory Bowel Disease from NewYork-Presbyterian/Columbia University Medical Center, where he completed his fellowship in gastroenterology. His research focuses on understanding the role of bacteria in inflammatory bowel disease, seeking to characterize an emerging class of innate lymphoid cells (ILCs) that regulate intestinal inflammation in IBD and assess the interaction of intestinal bacteria with ILCs. While at Columbia, Dr. Longman used biopsy samples from patients and advanced



Dr. Ellen J. Scherl

sequencing techniques to index all the bacteria attached to the intestinal mucosa, helping to characterize microbes and microbial communities important in ILC activation. "Using germ-free mice, as well as mice with specific genetic mutations, I ultimately hope to determine the particular signaling pathways required for ILC activation and provide insight into the therapeutic manipulation of ILCs in the clinical management of IBD," says Dr. Longman.

The individual and collaborative research underway in the Roberts Center is informed by the tissue bank and bio-bank established by Andrew J. Dannenberg, MD, the Henry R. Erle, MD-Roberts Family Professor of Medicine at Weill Cornell Medical College. Dr. Dannenberg is one of the world's leading authorities on the link between chronic

inflammation and cancer. His interest in gaining a clearer understanding of the mechanisms underlying the inflammation-cancer connection includes investigations in IBD, which can predispose a patient to colorectal cancer. Many of the pathways that are aberrant in colitis are also altered in colorectal tumors.

A Primer on IBD Pharmaceuticals

About 15 years ago, medical treatment for IBD began a transformation with the introduction of infliximab, the first medication of a new class of biologic drugs. "These drugs are antibody therapies that bind to tumor necrosis factor, a signaling molecule known to play a role in inflammation associated with Crohn's and ulcerative colitis," notes Dr. Scherl. "Until the advent of anti-TNF therapy, we could only offer treatment with steroids and the immunosuppressant azathioprine."

Since then, with improved understanding of the pathophysiology of IBD, many therapies have been added to the pipeline to target

Current Therapies for Moderate to Severe Ulcerative Colitis and Crohn's Disease

Class	Name of Drug	Status	Disease Target
Biologic – Anti-TNF	Infliximab	FDA Approval 1997	Crohn's Disease and Ulcerative Colitis
	Adalimumab	FDA Approval 2008	Crohn's Disease
	Certolizumab Pegol	FDA Approval 2008	Crohn's Disease
	Adalimumab	FDA Approval 2012	Ulcerative Colitis
	Golimumab	FDA Approval 2013	Ulcerative Colitis
Biologic - Anti IL-12/IL-23 Antibodies	Ustekinumab	Phase III Clinical Trial	Crohn's Disease
Anti-Integrin	Natalizumab*	FDA Approval 2008	Crohn's Disease after Failed Anti-TNF Therapy
	Vedolizumab	Final Phase of FDA Approval	Crohn's Disease and Ulcerative Colitis
Mesenchymal Stem Cells	Prochymal®	Phase III Clinical Trial	Crohn's Disease
Steroid	Uceris Budesonide MMX	FDA Approval 2013	Ulcerative Colitis

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Inflammatory Bowel Disease (continued from page 2)

specific molecules involved in the inflammatory process.

"Translational research – both investigator and industry initiated – in inflammatory bowel disease is rapidly evolving," says Dr. Scherl. "Different classes of drugs have been under study for many years, and we have participated in clinical trials for a number of them, collaborating with our GI colleagues across the country."

The newest drug to be added to the portfolio of IBD therapies is vedolizumab – a member of the anti-integrin class of drugs. Vedolizumab recently received a Priority Review Status and has just completed the final phase in the FDA approval process for the treatment of Crohn's disease and ulcerative colitis. Dr. Scherl and her team participated in the multicenter clinical trials that have brought vedolizumab to market. "This drug, which is gut-specific and gut-targeted, decreases inflammation in both ulcerative colitis and Crohn's disease by addressing the dysregulated recruitment of leukocytes into the intestine that is a characteristic feature of IBD," says Dr. Scherl. The results of the most recent phase III studies of vedolizumab have been published in *The New England Journal of Medicine*.

"This is an exciting time in therapeutic developments for inflammatory bowel diseases," says Dr. Scherl. "Medications, such as vedolizumab, enable us to offer patients alternatives if their IBD

is refractory to conventional treatment, resistant to one biologic over another, or if the medication prescribed has side effects that cannot be tolerated."

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For More Information

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Managing Eosinophilic Gastrointestinal Disorders in Children

A growing number of children and adults today are being diagnosed with eosinophilic gastrointestinal disorders (EGID), a chronic and complex group of diseases characterized by above normal amounts of eosinophil granulocytes – proinflammatory white blood cells – that are deposited in one or more places in the digestive tract. Eosinophils have roles in both host defense and pathological processes and they largely reside in the tissues, instead of the blood like neutrophil granulocytes.

"Eosinophilic esophagitis – one of several eosinophilic gastrointestinal diseases – was first described in detail as a distinct entity in 1995," says Aliza B. Solomon, DO, a pediatric gastroenterologist in the Division of Pediatric Gastroenterology and Nutrition at NewYork-Presbyterian/Komansky Center for Children's Health. "While we have had only a relatively short time to study this disease, the number of published reports and articles on EGID since 1995 has exploded."

According to Dr. Solomon, the prevalence of EGID points to environmental and food allergen triggers. "However, research is also looking into its genetic predisposition, and a few studies to date have, indeed, found some genetic markers. Like many of the other gastrointestinal diseases where there is some genetic predisposition triggered in association with an environmental stimulation, that can set off the development of the disease," explains Dr. Solomon.

While EGID affects people of all ages and ethnicity, males are slightly more prone than females. "There seems to be two groups where it increases in number and peaks – one is in children and the other is in adults, generally people in their 30s," notes Dr. Solomon. "We also do see a clustering in families. Sometimes when we diagnose the child, the parent starts thinking, 'maybe I have some subtle symptoms' or 'my other child has something' and it may lead to more

diagnoses. An adult may ignore symptoms, but when they see them in their child, they are more likely to seek an evaluation and diagnosis."

Symptoms of EGID range from feeding problems and poor weight gain to vomiting and diarrhea. "When we have children with varied presentations, it's very important that we obtain an accurate diagnosis and treatment plan to avoid potential complications," says Dr. Solomon. "We address it from a comprehensive, multidisciplinary, team approach where a gastroenterologist, allergist, and nutritionist are the primary guiders of the disease diagnosis and management plan. We arrange for patients to see all of these primary specialists in one visit, in one day. Then we incorporate our other team members as needed to help address the patient's complete care plan, which can include preventing nutritional deficiencies, coping with chronic illness, individualized school plans, and advocacy."

The team includes a pediatric anesthesiologist for diagnostic and therapeutic endoscopy, a pediatric pathologist, a speech and feeding therapist, and a pediatric psychologist to help the child or adolescent cope with a diagnosis that means a lifetime of chronic illness. "We also provide a pediatric patient navigator to coordinate multiple clinical appointments, individualize a school plan for a child who may have to avoid certain food products or environmental triggers, and to help with insurance matters," says Dr. Solomon.



Dr. Aliza B. Solomon

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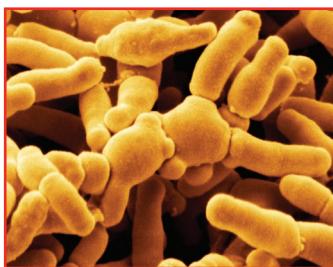
Establishing a Link Between Intestinal Flora and Adaptive Immunity

As a pediatric gastroenterologist with the Division of Gastroenterology, Hepatology, and Nutrition at NewYork-Presbyterian/Morgan Stanley Children's Hospital, and an affiliate member of the Columbia Center for Translational Immunology, Esi S.N. Lamousé-Smith, MD, PhD, integrates the worlds of basic science and clinical care effortlessly.

In the laboratory, Dr. Lamousé-Smith is helping to uncover a better understanding of how intestinal flora can impact immune system development and function through the establishment and utilization of infant mouse models. "I am looking at what might happen if a normal intestinal flora is disturbed or disrupted early on, with a particular focus on responses to infections or to immunizations, which many infants and children receive in the first year of life," says Dr. Lamousé-Smith. "I came to this through a clinical interest in probiotics, thinking about how probiotics potentially work and function in the context of what we already know about the microflora. In order to understand how probiotics may have an impact, we need to know what's present in the gut."

Understanding the Intestinal Microbiome

Dr. Lamousé-Smith began her work in this area about seven years ago – just around the time that interest in the gut microbiome really took hold in the research community – while pursuing fellowship training in pediatric gastroenterology at Boston Children's Hospital and in the lab of Michael Starnbach, PhD, at Harvard Medical School. "As a doctoral graduate student at the University of Pittsburgh School of Medicine my thesis work focused on cytotoxic T-lymphocytes, which we typically think of as having important properties for fighting infection and helping to manage or prevent the development of cancers. This is what generated my initial interest in systemic immune function. And, of course, being a pediatrician by training and involved in prescribing antibiotics in infants, particularly pre-term infants, got me thinking about how we may be affecting intestinal microflora in the first few weeks and years of life."



Bifidobacterium breve – a commensal bacteria that also has probiotic function

"The intestinal tract, in actual numbers of immune cells, is the largest immune organ in the body. Typically, the lymph nodes and spleen are considered the repository of T-cells, where "they hang out, waiting to respond to infection," explains Dr. Lamousé-Smith. "But that's not really the case. Investigators are now determining that many of our T-cells are also poised in the tissues of our intestinal tract – as first responders of a sort – to fend off invading organisms."



Dr. Esi Lamousé-Smith's background and training in cellular immunology and pediatric gastroenterology guided her to a specific interest in the role that the gastrointestinal flora plays in health and disease in children.

According to Dr. Lamousé-Smith, recent papers from other investigators have shown that, in fact, alterations in the gut biome in mouse models very much influence other mucosal tissue sites, particularly in the lungs. "Based on work done in adult mice, an altered microbiome in the gut may impact the ability to fight flu infection in the lung, modify responsiveness to allergens, and increase asthma susceptibility. So, in fact, changes in our gut – and the relationship between the microflora and the immune system in the gut – can have a wide-reaching impact in the rest of the body."

Pursuing Investigations in an Infant Mouse Model

What makes Dr. Lamousé-Smith's research unique is that she is focusing on a pre-weaning infant mouse model, rather than using adult mice, to address questions regarding the role of the intestinal microbiome during this important period of human development. "This may set the stage for future immune responses," she says. "If the gut is disturbed early in life, does it even matter...and does it matter only temporarily or permanently? And can it be fixed? These are the three questions that I'm trying to address."

Research in germ-free mice and mice treated with antibiotics to alter the intestinal flora has demonstrated an association with immune dysregulation and the development of allergic and autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease. "These observations indicate that the intestinal flora has broadly distributed effects on adaptive immune function and its regulation," notes Dr. Lamousé-Smith. "The exact mechanisms involved in mediating these effects are not yet entirely clear, and how gastrointestinal flora influences systemic adaptive immunity during this early period of development has not been well studied. Until recently, it has been generally accepted that antibiotic use causes only transient changes to the flora with no significant future consequence."

Dr. Lamousé-Smith is studying how infant and juvenile mice

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Intestinal Flora and Adaptive Immunity (continued from page 4)

treated with antibiotics at specific ages are able to fight infection or respond to immunization. Both of the experimental models that she is investigating are providing a platform to test the potential role of probiotic species in promoting, supporting, and potentially correcting immune dysfunction.

"The extent to which a balanced intestinal flora regulates systemic immune responses is still being defined," says Dr. Lamousé-Smith. "We are utilizing a model in which infant mice acquire an intestinal flora from their mothers that has been altered by broad-spectrum antibiotics to examine whether the acquisition of a less complex flora influences responses to immunization in the pre-weaning stages of life."

Using an antibiotic treatment mouse model, Dr. Lamousé-Smith seeks to replicate a real world circumstance. "Exposure to antibiotics happens to almost everybody during their lifetime, and to some people more than others. I believe that this model has more relevance than others in trying to determine the role of the gut flora in immune function. Ideally you want to have a mouse that's developed normally and had a chance to achieve a normal gut physiology and immune system, and then start manipulating the model."

Dr. Lamousé-Smith and her colleagues found that the infant mice with flora altered by an antibiotic had lower antigen specific antibody titers compared to control age-matched mice. In a second model, they examined germ-free mice to analyze how the complete lack of flora influences the ability to mount normal antibody responses following subcutaneous immunization.

"Germ-free mice do not respond well to immunization, and introducing a normal flora into these mice restores the capacity to respond," says Dr. Lamousé-Smith. "These results indicate

that a gastrointestinal flora reduced in density and complexity at critical time points during development adversely impacts immune responses to systemic antigens."

The Next Phase: Applying Laboratory Findings to Human Health

Moving into the translational aspects of her research, Dr. Lamousé-Smith is most interested in addressing the role that probiotics may have within this type of a model. "For example, when an infant receives antibiotics are they more or less at risk for infection soon after treatment because something has altered in their immune system? Can you prevent that from happening if you replace the flora that was temporarily altered by the antibiotic treatment? Can you treat an infant with probiotics and prevent an immunologic outcome? This is what I'd like to be able to test in my model as it has the potential for quite direct translational application."

According to Dr. Lamousé-Smith, this may also have potential applications for allergy treatment and prevention of allergies. "Understanding how a specific or multiple bacterial species may modify or prevent sequelae in immune system function if the gut flora has been altered, particularly during infancy and childhood, may be applicable to a lot of other specialties."

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For More Information

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Managing Eosinophilic Gastrointestinal Disorders in Children (continued from page 3)

Treatment for EGID is very effective, says Dr. Solomon, whether it is dietary or medical management. "The disease can go into remission and that is ultimately our goal. But it is chronic, so there is a high likelihood that it may relapse and potentially develop complications. That is why follow-up is so important."

The good news is that eosinophilic esophagitis is more responsive to dietary therapy than some of the other eosinophilic gastrointestinal diseases. "The most effective therapy is actually removing all proteins and it can respond tremendously," explains Dr. Solomon. "A dietary change can lead to response and resolution of both the clinical symptoms and from a tissue perspective, the actual inflammation."

For patients who do not respond to dietary changes, there are medical therapies, including systemic and topical steroids, which also are effective. "In children, more specifically, diet is a good option," she says. "Sometimes in adolescents and

adults, medication is a better choice from a lifestyle perspective."

The good news is that eosinophilic esophagitis is more responsive to dietary therapy than some of the other eosinophilic gastrointestinal diseases.

Dr. Solomon regularly speaks with general pediatricians in the region to make them aware of presentations that could be signs of EGID. "The pediatrician is really the first person that might see these complaints, and if they don't recognize certain warning signs, there may be a delay in diagnosis," she says. "Infants and young children cannot tell you they've got heartburn and describe that sensation, so it's important that the pediatrician asks parents about problems with feeding and eating."

Things to note include a delay in the normal milestones of feeding development or if the child is avoiding certain foods. Dr. Solomon notes that children with EGID tend to avoid big, chunky textures, or wash down food with fluid every time they take a bite. "If you don't ask targeted questions of the parent, you may assume that the child just hasn't developed yet."

Dr. Solomon is optimistic that research will discover more targeted therapies for EGID in the future. "Once we understand from a cellular perspective what generates the inflammation that ultimately triggers these eosinophils to be recruited in the esophagus, we will understand where the targeted therapeutic options are. These are the areas in which some of the medical therapeutic interventions are in the process of being tested," adds Dr. Solomon.

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A Multipronged Attack on Barrett's Esophagus

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or less likely to go on to get cancer. Right now we are using the same treatment recommendations for all patients with Barrett's. If we can determine who is at high risk, we can, hopefully, have a bigger impact."

The Current Standard in Clinical Intervention

NewYork-Presbyterian/Columbia – with five clinical investigators, several laboratories, and a team of study coordinators – has one of the largest clinical and research programs related

to Barrett's esophagus in the country. "On the clinical side this involves state-of-the-art tools and treatments for patients with pre-cancerous changes in Barrett's esophagus and early cancer of the esophagus," says Dr. Abrams. "We have a wealth of clinical experience in which Dr. Lightdale's practice is the cornerstone. He's one of the pioneers in this field."

In 2009, Dr. Lightdale was senior author of a multicenter study that assessed whether endoscopic radiofrequency ablation could eradicate dysplastic Barrett's esophagus and decrease the rate of neoplastic progression. "We believe that the most important patients to treat are those whose biopsy shows high-grade dysplasia," says Dr. Lightdale. "These patients are at the greatest risk of developing cancer. The 2009 paper went a long way to show that. We looked at patients with high-grade and low-grade dysplasia. In both cases disease progression was significantly reduced. If a patient has a nodule, we have to remove that first. That can be done with endoscopic mucosal resection. This provides a large pathology specimen that shows the depth of invasion [stage] and whether the lesion is completely removed. For the earliest stages of invasive cancer, where the cancer gets just into the mucosal lining, treatment with endoscopic mucosal resection is equally as safe and effective as for high-grade dysplasia, and avoids the need for esophagectomy."

"As a follow-up to that landmark study, we've started to do long-term studies to see how these patients do after radiofrequency



Dr. Julian A. Abrams

ablation," says Dr. Abrams. "We're also testing novel therapies for eliminating the Barrett's tissue. Instead of burning it with the ablation, we're using a cryotherapy device to freeze the tissue with a liquid nitrogen spray and another device that uses a special freezing balloon. The major advantage is, unlike with radiofrequency ablation, there's little to no pain. Both Dr. Lightdale and I think that this could be the future of the field. It's very new and we're just compiling data now, but we're very excited about it."

Seeking Answers in the Laboratory

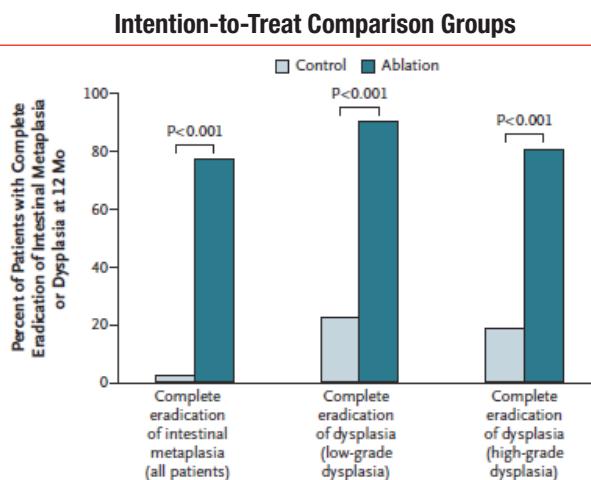
While clinicians are pursuing advances in preventing Barrett's esophagus from progressing to cancer, new ideas and discoveries are coming out of NewYork-Presbyterian/Columbia's laboratories under the direction of Timothy C. Wang, MD, Chief of the Division of Digestive and Liver Diseases. "Dr. Wang is an incredibly gifted scientist," says Dr. Lightdale. "He has developed a mouse model in which the mice develop conditions very similar to Barrett's esophagus and go on to develop dysplasia and cancer. It's an excellent model and we are using it to look at the types of cells involved. We think that if we can identify molecular markers related to these cells it would allow us to target the cells more specifically for cancer prevention."

According to Dr. Lightdale, high-grade and low-grade dysplasia are the best markers of risk of cancer in Barrett's esophagus at this point in time. "The problem right now is that these markers depend on the pathologists' interpretation of the biopsy, and they don't always agree. Determining high-grade dysplasia is more reliable, but there is a lot of variability among pathologists at the level of low-grade dysplasia. What we need is something more quantitative. We're looking very hard to come up with molecular markers that can be measured and provide a more definitive understanding of risk. This is work that is also coming out of the laboratory."

The goal of Dr. Lightdale and his colleagues is to identify markers for risk stratification. "This is a very important concept so that we can look at people with Barrett's esophagus, even if they don't have dysplasia on biopsies, and be able to say to them, 'You're not at risk; you don't have to worry about this at all.' And then the much larger group, perhaps 90 percent, does not have to worry. However, for the 10 percent that do, we'll follow them very closely and if their risk looks very high based on the markers, then we should ablate their Barrett's esophagus even though there is no dysplasia."

While the researchers doubt that one marker is going to be sufficient, they hope to develop a panel of markers that would help decide which patients are at risk. "You can say that this is our Holy Grail," says Dr. Lightdale. "I think it's going to happen because we are getting a lot of information about the abnormalities in the cells that seem to make patients with Barrett's at risk. I'm hopeful that within the next few years we'll have something that we can test in clinical trials."

In recent years, Dr. Wang's research group has uncovered some very noteworthy data in mouse studies that show that gastrin can potentially have an effect on Barrett's esophagus tissue that may promote cancer. "This is particularly interesting because all of the patients with Barrett's esophagus, since they have acid reflux, are on proton pump inhibitors, which boost the production of gastrin," says Dr. Abrams. "We're not saying that if you take a proton pump



Regardless of the level of dysplasia, patients who received radiofrequency ablation were significantly more likely than those in the control group to achieve complete eradication of dysplasia.

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Barrett's Esophagus (continued from page 6)

inhibitor that your risk of cancer goes up. Rather some people may have a more robust response to the drug where they'll produce more gastrin. Perhaps, in those patients, it may increase the risk. We're now enrolling patients in a clinical trial using a new drug that blocks the effects of gastrin."

Barrett's Esophagus Translational Research Network

Two years ago, to accelerate research in Barrett's esophagus, the National Institutes of Health established the Barrett's Esophagus Translational Research Network (BETRNet) – a research consortium comprised of bench-to-bedside investigators from NewYork-Presbyterian/Columbia, the Mayo Clinic, and the Hospital of the University of Pennsylvania. Each of these tertiary referral centers has a very large patient population with Barrett's esophagus, clinical investigators focused on Barrett's, and bench researchers with extensive experience in stem cell and inflammatory models of gastrointestinal cancer.

"This consortium was designed to have multidisciplinary, multicenter, and collaborative work based in both the laboratory, as well as in the clinical setting," notes Dr. Abrams. "The goal is largely to identify how Barrett's esophagus forms in patients, which Barrett's patients are at risk for getting cancer, and how can we ultimately prevent that from happening. And we are looking for optimal treatments for patients who have already developed advanced pre-cancerous changes or early cancer."

"We also are trying to find out who will respond to treatment and who will have recurrence of disease following treatment," adds Dr. Lightdale. "After we ablate the abnormal lining, we keep patients on an acid-blocker medication. A new lining grows back that is normal. If we can understand that process better, it may give us a clue to how the reverse happens – how the normal lining gets injured – and lead to an understanding of how we can help prevent the Barrett's from occurring. We know in some patients that the conditions that cause the Barrett's to develop in the first place are still present. Treatment doesn't really change the anatomy, and a percentage of patients, maybe one in five, has a risk of abnormal cells returning. That is why we continue to follow these patients and treat them again as needed. We think that if we can keep patients free of Barrett's then their risk of developing cancer will be decreased; however, we have to prove that with longer-term studies."

To aid in this effort, the BETRNet consortium and NewYork-Presbyterian/Columbia have established a database with more than 1,000 Barrett's esophagus patients enrolled to date containing clinical information, as well as tissue and blood. "We're keeping these in a bank so that when new discoveries come out of the laboratory we can use these materials to support testing," says Dr. Lightdale. "At the same time we're following these patients so that we know what happens to them. We'll know which of them is going to develop dysplasia and which of them won't. We can also look at these patients from a clinical point of view, for example, to see if these are patients who are obese or if they're patients who've had a history of smoking. We have all of this information stored."



Dr. Timothy C. Wang

Through BETRNet, investigators at all three sites are able to pool database resources along with their expertise to address a number of issues. One study, recently published in *Gastroenterology*, looked at the recurrence of intestinal metaplasia after successful radiofrequency ablation, with a specific focus on estimating the incidence of return and prediction factors. The group analyzed data from 592 patients with Barrett's esophagus treated with radiofrequency ablation between 2003 and 2011 at their respective institutions. "We defined complete remission as eradication of intestinal metaplasia in esophageal and gastroesophageal junction biopsy specimens and documented by two consecutive endoscopies," explains Dr. Lightdale. "Recurrence was defined as the presence of intestinal metaplasia or dysplasia after complete remission as seen in surveillance biopsies."

The study showed that 56 percent of patients were in complete remission after 24 months. However, 33 percent of these patients had disease recurrence within the next two years.

"Most recurrences were nondysplastic and endoscopically manageable, but this confirmed that continued surveillance after radiofrequency ablation is essential," he says.

On the Horizon

One of the major challenges for clinicians is in identifying patients at risk much earlier. "The big problem we have right now is that most patients who present with esophageal cancer present at an advanced stage, which is very difficult to cure," says Dr. Lightdale. "We'd like to identify patients who are unaware that they are at risk because they don't know that they have Barrett's esophagus. Not all patients with Barrett's have severe reflux symptoms that prompt them to see a doctor. We are screening patients for Barrett's esophagus with ultra-thin trans-nasal endoscopy that can be done without sedation, and will also be testing new pill-size screening devices that can be easily swallowed."

Drs. Lightdale, Abrams, and their colleagues are pursuing studies with state-of-the-art endoscopic imaging devices, including narrow band imaging, confocal laser endomicroscopy, and optical coherence tomography, to facilitate the detection of dysplasia or early cancer. Adds Dr. Abrams, "These devices, which are not readily available outside tertiary care centers, are thought to be very important for maximizing our ability to find changes in the tissue."

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