

A Re-Look at Intussusception in Childhood

It is generally understood that most cases of intussusception occur during infancy, and there appears to be an association with viral gastroenteritis, including Rotavirus infection. The authors of this study performed a prospective observational study of pediatric intussusception cases in 38 pediatric clinical sites in Switzerland as part of the Swiss Pediatric Surveillance Unit, an epidemiologic group which evaluates causes of childhood hospitalizations. A study questionnaire was sent to all sites to record various aspects of intussusception including patient demographics, mode of diagnosis, treatment type, and outcome over a three-year period.

A total of 288 cases were available for evaluation with 67% of study subjects being male. The mean age at diagnosis was 2.7 years, and infants less than 12 months of age represented the largest group. However, the total number of affected infants was much less than the total number of older patients when compared to previous studies. Only 24% of children had a history of acute gastroenteritis and association with Rotavirus was rare. Abdominal pain, vomiting, and pallor were common presenting symptoms while an appreciable abdominal mass and the presentation of the classic “currant jelly stool” was less common. Treatment outcomes demonstrated that 13% of patients had spontaneous resolution of intussusception while 63% of patients required hydrostatic reduction via enema and 23% required surgery. All patients recovered without complications.

This study differs from previous intussusception epidemiologic studies in that there was no strong association with acute gastroenteritis or Rotavirus infection. Also, there appeared to be no seasonality of cases suggesting that Rotavirus was not a common cause as Rotavirus infection has a tendency to peak in December and April in Switzerland. Finally, although the highest incidence of intussusception occurred in infants, this recorded incidence was lower than epidemiologic studies from other countries.

This study suggests that the existing paradigm regarding intussusception incidence rates and age of presentation may be inaccurate and changing. The lack of strong association with Rotavirus infection is intriguing suggesting that the new Rotavirus vaccines are both effective and safe. (Buettcher M, Baer G, Bonhoeffer J, Schaad U, Heininger U. “Three-Year Surveillance of Intussusception in Children in Switzerland.” *Pediatrics*, 2007; Vol. 120: 473-480).

Food Allergy and Timing of Solid Food Introduction in Children

It is usually recommended that infants avoid solid food introduction until six months of age, in order to prevent the development of food allergies. However, the data to support this belief comes from small studies. The authors of this study used data from the German Infant Nutritional Intervention Program (GINI) which evaluated the development of eczema in two distinct regions of Germany. The patients were randomized into two groups which included an intervention group with a family history of atopy and who breast fed for the first four months of life before converting to a hydrolyzed or cow’s milk-based formula. The non-intervention group had no family history of atopy. Basic questionnaires regarding family allergy history, maternal smoking, pet contacts, and feeding practices were obtained, and patients were followed for the development of eczema.

Significantly more patients in the intervention group had eczema, and interestingly, these patients were introduced to solid food later in infancy. These patients also had a decreased diversity of food product exposure. This finding is different from the current prevailing thought that infants are less likely to develop allergic disease if they are exposed to food later in infancy and if they are initially introduced to a small variety of food. There also appeared to be a trend for increased eczema in the intervention group if they were exposed to meat products in the second half of the first year of life.

The current recommendations for introduction to solid food during infancy has been poorly researched, and this study demonstrates that delayed introduction of solid foods may not prevent allergic disease. More clinical research is needed in this area, although it is still appropriate to recommend avoidance of solid food meals very early during infancy to prevent other hazards such as choking and aspiration. (Filipiak B, Zutavern A, Koletzko S, Von Berg A, Brockow I, Grühl A, Berdel D, Reinhardt D, Bauer C, Wichmann H, Heinrich J, and the GINI-Group. “Solid Food Introduction in Relation to Eczema: Results from a Four-Year Prospective Birth Cohort Study.” *J Pediatrics*, 2007; Vol. 151: 352-358).

John F. Pohl, MD, editor of “From the Pediatric Literature” is Assistant Professor of Pediatrics, Section of Pediatric Gastroenterology at Scott & White Memorial Hospital and Clinic, Temple, TX.

***Colorectal Cancer: Evidence-Based
Chemotherapy Strategies***

Saltz LB, Editor

Humana Press, Totowa, New Jersey, 2007

ISBN: 1-58829-751-9; \$ 99.50

Treatment options for colorectal cancer (CRC) patients have undergone a significant sea change in the last ten years. Barely one decade ago, 5-FU was essentially the only drug approved for treatment of metastatic CRC or for treatment in the adjuvant setting. Today, clinicians can choose from over a half dozen approved agents for metastatic disease with a number more in clinical trials.

This volume of approximately 280 pages serves as an excellent current monograph on colorectal cancer treatments. Each of its 15 chapters, all well referenced, can easily stand alone as the 2007 definitive discussion of each chapter's respective topic. With discussions ranging from cytotoxic chemotherapy to antiangiogenic strategies, to treatment of limited metastatic disease, this volume has an authoritative feel and tone to it. Edited by Leonard Saltz, M.D., of Memorial Sloan-Kettering Cancer Center in New York, the list of authors represents outstanding researchers in their respective fields ranging from molecular biology, medical oncology, diagnostic radiology, and nursing. The authors speak to the tremendous research over the past quarter century that has now resulted in marked improvement in treatment options for CRC patients. Each author hails from a major academic medical center and highlights much of the work that is being done at their respective institutions as well as collaboratively through clinical trials.

Few areas in clinical oncology have been as revealing at the basic science level as CRC. The opening chapter on molecular biology of colon cancer explains the remarkable progress that has been made in understanding the genetic and epigenetic alterations that have been described in disease causation. William Grady's discussion points to the various signaling pathways, alterations at the molecular level, genetic missteps, genomic instability, and alterations in gene expression that lead the process of colon carcinogenesis. With regards to the insights in Brady's discussion on the mechanisms of tumorigenesis, at each step, he points to potential therapeutic options as well.

Although the field of chemoprevention is well dis-

cussed in the second chapter, it is clear that this area has less of the rigor that is introduced in the chapter on molecular biology of CRC. Through carefully controlled clinical trials, the notions of increased fiber and antioxidant supplements being associated with reduced polyp/cancer outcomes are debunked. Although there are some good data for individuals predisposed to CRC that NSAIDs such as aspirin and selective COX-2 inhibitors can reduce polyp incidence and presumably the incidence of CRC, the time frame and difficulty in conducting such trials is daunting and not likely to soon yield dramatically new information.

In the chapter on screening and surveillance, Arnold Markowitz details the current strategies for detection and follow-up with special emphasis on guidelines for those at increased risk such as patients with inflammatory bowel disease and hereditary colorectal cancer syndromes.

As to chemotherapy, the succeeding seven chapters highlight the remarkable success for treating CRC, both in the metastatic and in the adjuvant settings, that has been accomplished in the last decade via the clinical trials process. Perhaps most significant in this discussion has been the elucidation of novel biologic agents as well as the anti-vascular endothelial growth factor (VEGF), bevacuzumab, and anti-epidermal growth factor receptor, cetuximab. This area is a rapidly unfolding part of the story of CRC and patients should be encouraged to participate in further clinical trials to address such issues as the role of anti-angiogenesis agents in the adjuvant setting and in rectal cancer. The perturbations of options available for individual patients will remain a challenge until newly launched clinical trials mature (and likely open new questions to be addressed).

Management of liver metastasis is deftly handled in two chapters, one looking at the rationale for adjuvant and neoadjuvant chemotherapy in the resection of liver metastasis, and the second dealing with radiofrequency ablation (RFA) for metastatic disease. Such treatment approaches need to be individualized as there obviously is an absence of data from prospective clinical trials in dealing with this problem. The chapter on RFA is a particularly good summary with good quality photographs.

(continued on page 50)

(continued from page 48)

Rounding out this volume is a potpourri of practical topics: imaging, nursing issues, and pain management. The final chapter, a look to the future, brings us back full circle to the first chapter on molecular biology of CRC and discusses novel agents and how the advent of molecularly targeted therapies have fundamentally changed how we will treat CRC in the future.

Overall, this is a very readable volume where, for the most part, each chapter can stand alone on its respective topic. The only criticism is that this format is likely to be out of date in a relatively short time as the basic science information and translational research in CRC is moving rapidly.

Tim Grennan, M.D.
Sacramento, CA

Pancreas: Pathologic Practice and Research

Suda K, Editor

Karger, Basel, Switzerland, 2007

ISBN: 978-3-8055-8240-7; \$180

This book is an excellent review of the embryology, pathogenesis and pathology of different pancreatic disorders. It touches several keen areas of pathology in various pancreatic disorders ranging from congenital anomalies to inflammatory and malignant problems with the pancreas.

The first chapter details on the embryology of the pancreas to enable the readers to refresh their memory and better understand the congenital anomalies and put them in clinical perspective.

The second chapter explains the vascular anatomy of the pancreas, which helps us understand the pathogenesis in acute pancreatitis and helps us understand the mechanism of the disease and so the treatment modalities of benign and malignant pancreatic disorders.

The next few chapters explain the mechanisms and pathology of pancreatic fibrosis, chronic pancreatitis, and autoimmune pancreatitis. The sections on precancerous and carcinoma of the pancreas are very well done.

Though the images are black and white, the quality of pictures are good. This book is an extensive review of the pancreatic pathology, which helps develop novel ideas on treatment modalities, as we understand the pathology better.

This book will of specific interest to many medical personnel including but not limited to gastroenterology fellows, pancreatic researchers and pathologists.

Vasu Appalaneni, M.D.

Wright State University School of Medicine
Dayton, OH

Textbook of Hepatology: From Basic Science to Clinical Practice, Third Edition

Rodes J, Benhamou J-P, Blei AT, Reichen J, Rizzetto M, Editors.

Blackwell Publishing, Malden, MA, 2007

ISBN: 978-1-4051-2741-7; \$725

The third edition of the *Textbook of Hepatology* is a superb reference and sets the standard for hepatology textbooks in both content and quality. This edition has been considerably expanded with many new authors, new sections, and more extensive discussions of liver function, pathobiology, mathematics in liver disease, and clinical assessment of liver disorders to name a few. New chapters such as the one on herbal preparations and liver injury will be of value to each of us who struggle with the surge of herbal preparations in use by our patients and the need to understand their role in the pathogenesis of our patients liver disease. Past chapters have been updated or completely re-written by new authors. The section on liver transplantation has gone from a single chapter to a large section of many topics. The grouping of topics in many sections has also been altered with good effect. References for chapters are up to at least the year 2004 with many chapters having references from 2005. In addition, common references are no longer scattered throughout the text and instead are included at the end of each section. In general, I found the contents well-presented and I believe more readable. I also found the style of each chapter improved as well. I was especially drawn to the appearance of each page which was very reader friendly with black section titles and rose-colored subsection titles. Illustrations are ample but not overwhelming. Liver histology is presented in black and white plates but that is not a problem as the intent of this textbook is its content and not as a textbook of histology. You will enjoy just sitting down to peruse each chapter to expand your knowledge. While I can go on

and on with accolades, the bottom line is that you need this on your clinic desk as a reference if you practice gastroenterology or hepatology. If you are a primary care physician, you should at least make sure your hospital has a copy in its reference collection. You and I will learn much from reading this outstanding textbook of liver disease.

Rowen Zetterman, M.D.
Omaha, NE

Practical Pediatric Gastrointestinal Endoscopy

Gershman G. and Ament M.
Blackwell Publishing, Ltd. 2007.
ISBN: 9781405131933; \$175

This text proposes to provide detailed instructions on all practical aspects of diagnostic and therapeutic endoscopy procedures in children. Though not expressly stated, the intended audience is likely to include anyone who desires to perform endoscopy in children, such as the inexperienced pediatric gastroenterologists, pediatric gastroenterology fellows, pediatric surgeons, pediatric surgery fellows, adult gastroenterologists, or others willing to embark on such a challenge. Both the primary authors as well as the contributors are well qualified in this field to write such a book. However, the final result falls short of goals.

Given the similarity of the title to the highly regarded *Practical Gastrointestinal Endoscopy, The Fundamentals* by Peter B. Cotton and Christopher B. Williams (\$207.95), and the similarity in chapters, a comparison is natural. While the Cotton and Williams text abounds with cartoons to illustrate concepts, the Gershman and Ament book relies on word descriptions, which forces the reader to visualize the ideas. The former also frequently employs bullets and italics, that help organize the thoughts into discrete steps, while the latter uses flowing text in describing various complex scope maneuvers. Additionally, the former provides CD-ROM's; the latter has none.

I commend the authors for providing tables for equipment troubleshooting; I would encourage them to construct similar tables or flowcharts for patient-related problems (pre, during, and post procedure). Further-

more, I suggest that the authors define an optimal skill set for a pediatric endoscopist, an assessment/standard of initial competency for pediatric endoscopy, and a method of monitoring safety and quality outcomes. As a practical matter, it would be helpful to include both ICD-9 codes and CPT codes and examples of how to correctly bill multiple procedures.

Overall, I feel that this book is a bit overpriced compared to the Cotton and Williams book. Hopefully the next edition will be worth the cost.

Richard Quan
Sacramento, CA

Images of Memorable Cases: 50 Years at the Bedside

Fred HL and van Dijk HA
Long Tail Press/ Rice University Press 2007
ISBN: 978-0-89263-002-8
\$85.50 (perfectbound), \$160 (laminated textbook binding), \$165 (clothbound)

What ever happened to the art of physical diagnosis? It has been diluted by all of our technology. Dr. Fred and Mr. van Dijk have compiled 154 cases for the interested clinician to challenge himself/herself. Each case has a brief history and a photo or two of pertinent physical findings. On each overleaf is a brief discussion of the photo and the diagnosis.

The photos are high quality. The explanations are brief but pertinent. I enjoyed quickly reading through the book while on a cross country flight. Several similar cases are placed throughout the book as an opportunity to reinforce some key points. I plan to keep it at my bedside and refer to it frequently. Gastroenterologists will enjoy being challenged by such diagnoses as hereditary hemorrhagic telangiectasia, achalasia, pyoderma gangrenosum, pseudomyxoma peritonei, etc.

This book is a must for all residency programs in Internal Medicine and Family Practice. It would go well on most hospital libraries. This is so good I would suggest they try to put together a second volume.

George Meyer, M.D.
Sacramento, CA

George W. Meyer, M.D., Book Editor, is on the Editorial Board of *Practical Gastroenterology*.

T vs. B: Re-engineered Human T Cells Effectively Target and Kill Cancerous B Cells

Human white blood cells, engineered to recognize other malignant immune cells, could provide a novel therapy for patients with highly lethal B cell cancers such as acute lymphoblastic leukemia (ALL), according to researchers at Memorial Sloan-Kettering Cancer Center (MSKCC). By administering repeated doses of T cells designed to express an artificial receptor which recognizes human B cells, the researchers were able to eradicate cancer in 44 percent of mice bearing human ALL tumors.

Their findings, published in the September 15 issue of *Clinical Cancer Research*, a journal of the American Association for Cancer Research, show that modified T cells—the white blood cells that actively fight infections—can be effective in fighting malignancies associated with B cells (immune cells that create antibodies) such as chronic lymphocytic leukaemia (CLL), ALL, non-Hodgkin's lymphoma (NHL). The researchers have an ongoing study using these T cells in CLL, and have recently begun the planning stages for a trial in patients with ALL.

“The immune system has evolved to police the body for infections and diseased cells, but it has a difficult time recognizing malignant cells since they largely appear normal to the immune system,” said lead study author, Renier J. Brentjens, M.D., Ph.D., medical oncologist in the Leukemia Service at MSKCC. “The idea is that we can take a patient's own T cells, re-educate them by inserting a gene into them that will enable them to produce a receptor to recognize B cell cancers, and then return them to the patient where they should be able to attack and kill the tumor cells.”

Because the technique uses a patient's own T cells, there is little risk of compatibility issues or rejection, as there might be with human stem cell transplant, Dr. Brentjens adds. Human stem cell transplant, following radiation or chemotherapy, is currently incorporated into the treatment of several B cell malignancies.

In order to get T cells to recognize B cells, Dr. Brentjens and his colleagues created a gene that encodes for a cell-surface protein—an artificial T cell receptor called a chimeric antigen receptor—designed to specifically bind to CD19, a molecule found on the surface of B cells and B cell cancers. Antigen receptors

are what allow T cells, in combination with other parts of the immune system, to recognize and attack infected or malignant cells. This chimeric gene, formed from active portions of several immune system-related genes, creates the chimeric antigen receptor protein called 19-28z, which does not require other co-stimulatory signals to fully activate T cells, according to Dr. Brentjens.

Dr. Brentjens and his colleagues used an engineered retrovirus to insert the chimeric antigen receptor gene into T cell DNA. Retroviruses insert DNA derived from their RNA into that of a host cell, which then uses viral vector-encoded genes to make specific proteins. In this case, the researchers infected healthy T cells with modified retroviruses containing the gene that codes for 19-28z. The T cell's internal protein-making facilities then produce the chimeric receptor as if it were one of its own natural antigen receptors.

In *Clinical Cancer Research*, the MSKCC researchers detail the creation of 19-28z, their “second generation” chimeric antigen receptor, and its effectiveness in stimulating human T cells both in culture and in an animal model of human cancer. They also compared T cells engineered with 19-28z to T cells engineered with a “first generation” chimeric antigen receptor, lacking the co-stimulatory signal found in 19-28z. Their results showed that the “second generation” 19-28z receptor was superior to the “first generation” receptor, and that this T cell therapy works best when administered to mice through multiple weekly injections.

“The repeated boosts of new T cells during therapy to improve T cell persistence enhances the efficacy of these T cells in eradicating cancerous B cells,” said Dr. Brentjens. “This concept of T cell persistence being critical to treatment efficacy is one we are further investigating in current and upcoming clinical trials.”

The results have given the researchers further evidence that the technique will work in humans. When transplanted back into a patient, these engineered T cells could then attack and kill tumor cells bearing the CD19 protein. “CD19 is not found on the surface of bone marrow stem cells, so these modified T cells are reasonably safe since they should not attack other blood forming cells in the bone marrow following treatment,” Dr. Brentjens said.

(continued on page 54)

(continued from page 52)

Based on the results of their findings, the MSKCC researchers are currently conducting a clinical trial using this method in patients with chemotherapy-resistant CLL. CLL is currently considered an incurable cancer, Dr. Brentjens said, although the disease generally progresses slowly.

This research was funded by the Annual Terry Fox Run for Cancer Research, the Commonwealth Cancer Foundation for Research and the Experimental Therapeutics Center of MSKCC, the Alliance for Cancer Gene Therapy, an Amgen Career Development Award, The National Cancer Institute and the Bocina Cancer Research Fund

New Healthcare Codes to Leverage Doctor-Patient Relationship Codes Will Mainstream Substance Use Screening and Intervention in Healthcare Settings

The White House Office of National Drug Control Policy (ONDCP) has announced the publication of new healthcare codes for substance abuse screening and brief intervention (SBI). The new Current Procedural Terminology (CPT®) codes, issued by the American Medical Association (AMA), will make it possible for the health care system to efficiently report screening services for drug and alcohol abuse. The process will increase the likelihood that those with substance use disorders will receive an appropriate intervention, thereby reducing the number of patients

with substance use disorders. This is the first time that a physician can dedicate both time and resources to assess their patients' risky substance use characteristics and behaviors. The new healthcare codes will go into effect on January 1, 2008.

“Substance use is one of the most significant public health challenges in the United States,” said Deputy Director Dr. Bertha K. Madras. “Drug and alcohol use adversely affects the health and well-being of individuals, families, and communities, and costs billions of dollars every year in healthcare costs, as well as legal and workplace expenses. These new healthcare codes will strengthen the doctor-patient relationship, and incorporate a powerful preventive public health resource in America’s healthcare system. Doctors will now be able to assess their patients’ drug and alcohol use—as they already do for diabetes and obesity—and work to prevent, reduce, and treat those with substance abuse disorders.”

The AMA published the new procedural codes, providing medical professionals a means to communicate concisely and reliably with colleagues, patients and insurers about screening for substance use and appropriate interventions. Doctors and other medical professionals will now be able to ask their patients a series of questions (see sample) designed to provide an on-the-spot assessment of drug and alcohol use, and if necessary, offer immediate intervention.

“Today, there are an estimated 22 million Americans who abuse or are addicted to drugs or alcohol,” continued Dr. Madras. “Of these, nearly 95 percent of them are unaware that they meet the clinical criteria for substance abuse or addiction, and have not sought treatment. These new codes will enable physicians to reach those in harm’s way - during a doctor’s visit - and provide them with appropriate medical services. Widespread screening and brief interventions can effectively reduce substance use disorders and their adverse effects on the human brain, body, and behavior. Brief interventions are medically reliable, cost-effective, and endure.”

The new AMA Level I CPT® Codes for medical services were published October 8, 2007, and will become fully effective in January 2008. The two codes (99408 and 99409) will streamline reporting and the reimbursement procedure for doctors who perform



alcohol and/or substance (other than tobacco) abuse structured screening and brief intervention.

“The new procedures outlined by these codes can have a positive impact on every American touched by substance use, and seen in the healthcare system,” concluded Dr. Madras. “Screening and brief interventions can keep patients healthier, improve physicians’ performance measures, and reduce hospital and health-care costs. Implemented properly, screening and brief intervention is the most transformative substance use tool for medicine in decades.”

Below are some sample questions from the Drug Abuse Screening Test (DAST) that doctors may use to perform a SBI with their patients:

- Can you get through the week without using drugs?
- Are you always able to stop using drugs when you want to?
- Do you ever feel bad or guilty about your drug use?
- Have you neglected your family because of your use of drugs?
- Have you been in trouble at work because of your use of drugs?
- Have you engaged in illegal activities in order to obtain drugs?
- Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?
- Have you had medical problems as a result of your drug use (e.g., memory loss, hepatitis, convulsions, bleeding, etc.)?

For more information, please visit: <http://www.whitehousedrugpolicy.gov/>.

Researchers Find Significant Differences in Cancer Stage Presentation Between Rural and Urban Patients

New research published in the November issue of *The Journal of the American College of Surgeons* shows that urban colorectal and lung cancer patients present at later stages of disease than rural patients do. This finding is contrary to the common assumption that rural patients with cancer present at a later stage of disease in comparison with urban patients.

“The proportion of urban patients presenting with metastatic cancer is alarming,” said Ian Paquette, MD

at Dartmouth-Hitchcock Medical Center, Lebanon, NH. “This study highlights the need for better screening efforts for colorectal cancer and the need to develop an effective screening program for people at high risk for lung cancer.”

A retrospective, descriptive analysis of cancer stage at presentation was conducted to determine the relationship between stage of disease and whether patients lived in rural or urban areas. Lung cancer patients (161,479) and colorectal cancer patients (129,811) from 2000 to 2003 were identified in the Surveillance, Epidemiology, and End Results (SEER) database. Rural versus urban designations were based on rural-urban continuum codes (RUCC) from the US Department of Agriculture.

Overall, the study indicated that urban patients are presenting with later stages of colorectal and lung cancers when controlling for the other demographic factors associated with late presentation ($p < 0.001$). Notably, rural colorectal cancer patients were older and considerably poorer than urban patients, while urban colorectal cancer patients were considerably more likely to be language-isolated, African American, and divorced. Rural lung cancer patients were considerably poorer than urban patients, and they were more likely to be men. Urban lung cancer patients had demographics equivalent to the urban colorectal patients.

Although several factors, including race, socioeconomic status, age, and divorce, had an influence on stage at presentation, rural residence was not shown to be an independent predictor of later-stage disease.

New Minimally Invasive Sampling Technique Allows for Earlier Diagnosis of Pancreatic Cancer

A new optical technology, coupled with routine endoscopy, may enable doctors to detect the subtle tell-tale traces of early pancreatic cancer, according to researchers at Northwestern University in Illinois. The optical technology, developed by biomedical engineers at Northwestern exposes cellular changes indicative of cancer in tissue near the pancreas that had previously

VISIT OUR WEB SITE AT
PRACTICALGASTRO.COM

been detectable only through intensive radiologic scanning or invasive surgery, two techniques that can put pancreatic cancer patients at risk.

The results of the pilot study, presented in the August 1 issue of *Clinical Cancer Research*, a journal of the American Association for Cancer Research, could represent a new approach to detecting pancreatic cancer at a very early stage, when treatment is most likely to succeed.

“Pancreatic cancer is not often detected early because it is a rather inaccessible organ, so this technique holds the potential to be the first reliable, routine screening tool for pancreatic cancer,” said co-author author Randall Brand, M.D., an associate professor of medicine at Northwestern University and clinician at Evanston Northwestern Healthcare. “If we could apply this to those at high risk—such as people with chronic pancreatitis or who have a family history of pancreatic cancer—we might see a drastic improvement in pancreatic cancer survival.”

Pancreatic cancer is one of the leading causes of cancer death in America—over 33,000 Americans will likely die from pancreatic cancer in 2007, according to projections from the American Cancer Society. The five-year survival rate for pancreatic cancer is less than five percent of all cases. However, if caught at an early stage, available treatments cause the five-year survival rate to jump 10-fold to 50 percent, Dr. Brand said.

Although the pancreas is a difficult organ to study, the researchers took advantage of the so-called “field effect” of pancreatic cancer, where cancerous tissue exerts subtle physical changes in surrounding tissue. In an examination of 51 patients using tissue sampled through upper endoscopy (a minimally invasive procedure that entails the placement of an endoscope down the throat and through the stomach to the duodenum), the researchers were able to identify those patients with pancreatic cancer from the control group with a 95 percent accuracy. Importantly, the researchers could identify all 10 patients with early stage tumors that could be removed surgically.

“If we could reliably detect the presence of cancer prior to our ability to visualize it with our current imaging studies such as a CT scan or MRI, we would then have the justification to pursue aggressive surgical options,” Dr. Brand said.

The optical technology used to detect the field effect of pancreatic cancer was developed by the senior author of the study Vadim Backman, Ph.D., a professor of biomedical engineering at Northwestern along with his graduate student, Yang Liu, Ph.D, the first author on the report. With a single instrument, Backman can use two different means of detecting the optical properties of a tissue sample, both of which were developed in his laboratory: four-dimensional elastic light scattering fingerprinting (4D-ELF) and low-coherence enhanced backscattering spectroscopy (LEBS).

In essence, the 4D-ELF/LEBS instrument shines an intense white light onto a tissue sample and then measures how cellular structures on the micro- or nanoscale (on the order of a billionth of a meter) refract the light, causing it to scatter in different directions. Computer analysis of the scatter patterns can then determine if these cellular structures are different than those seen in structures within “normal” tissue. The researchers looked for the same optical changes that had been identified in a colorectal cancer study by Backman and Hemant Roy, M.D., an associate professor at Northwestern University and clinician at Evanston Northwestern Healthcare.

“We are able to use the optical properties of a cell’s structure to serve as a marker for disease,” said Backman. “These are changes within the tissue that cannot be detected through any other means. Neither antibodies nor diagnostic assays can detect them.”

According to Backman, optical markers are independent of other factors within the tissue microenvironment. “The markers do not change if the patient is a smoker. And the markers do not change with the location, stage or size of the tumor in the pancreas,” Backman said.

With the success of the pilot study, the researchers are currently involved in a larger study of the technique and its refinement. They estimate that the technology may be put into practice within three years.

Additional co-authors include Vladimir Turzhitsky and Young Kim of Northwestern University and Hemant Roy, Nahla Hasabou, Charles Sturgis, Dhiren Shah and Curtis Hall of Evanston-Northwestern Healthcare.

The study was supported by funding from the National Science Foundation and the National Institutes of Health.

Reactivation of Hepatitis B After HBe Antigen Seroconversion

A total of 133 HBeAg-positive, asymptomatic carriers who had undergone HBe seroconversion were studied. Reactivation of hepatitis B was defined as elevation of ALT greater than two times the upper normal limits, accompanied by serum hepatitis virus, DNA detectable by hybridization assays. The samples consisted of 75 men and 58 women and the mean age at entry was 28.2, ± 6.9 years. One hundred eight subjects had genotype B and 25 had genotype C.

The maximal ALT levels during the HBeAg-positive phase were less than two, two-to-five and greater than five times upper normal limits in 49, 40 and 44 subjects, respectively.

HBeAg seroconversion occurred after a mean follow-up of 4.6, ± 3.7 years during a mean follow-up of 5.8, ± 4.6 years following HBeAg seroconversion. Reactivation of hepatitis B occurred in 26 patients at 3.3 percent per year. Multivariate analyses demonstrated the reactivation of hepatitis B correlated significantly with genotype C, male sex, ALT levels greater than five times the upper limits of normal during the HBeAg-positive phase and age at HBeAg seroconversion greater or equal to 40 years.

It was concluded that at baseline, genotype C and male sex are independent factors predictive of reactivation of hepatitis B. Additionally, the likelihood of reactivation of hepatitis B is increased if more rigorous, immune-mediated hepatocytolysis or more prolonged immune clearance phase is necessary to eliminate the virus. (Chu, C.M., Liaw, Y.F. "Predictive Factors for Reactivation of Hepatitis B Following Hepatitis Be Antigen Seroconversion in Chronic Hepatitis B." *Gastroenterology*, 2007; Vol. 133, pp. 1458-1465.)

Genotypes of Hepatitis B and Clearance of Hepatitis Be Antigen

In order to analyze clearance of HBeAg, taking into account age and genotype, a prospective cohort study of 1,158 Alaska native persons throughout Alaska were tested serially for HBeAg for median of 20.5 years and were genotyped. Initial and final HBeAg-positive specimens, time to clearance, age at clearance

and subsequent HBeAg results were analyzed for persons initially HBeAg-positive. Subsequent HBeAg results were analyzed for persons initially negative.

Genotypes A, B, C, D and F were identified. Genotype C persons initially HBeAg-positive were more likely than those with other genotypes to be positive on initial and final specimens and time to HBeAg clearance was longer. Age at which 50 percent of persons cleared HBeAg was less than 20 years for those infected with genotype A, B, D and F, and 47.8 years in genotype C.

After losing HBeAg, those with genotype C and F were more likely to revert to the HBeAg-positive state.

It was concluded that genotype may have a strong effect on mode of transmission and outcome. Genotype C may have been responsible for most perinatal transmission, given that seroconversion from HBeAg occurs decades later than in other genotypes. (Livingston, S.E., Simonetti, J.P., Bolkow, L.R., et al. "Clearance of Hepatitis Be Antigen in Patients With Chronic Hepatitis B and Genotypes A, B, C, D and F." *Gastroenterology*, 2007; Vol. 133, pp. 1452-1457.)

HIV and Hepatitis C

The association of HIV and antiretroviral therapy (ART) with liver disease in patients with HCV infection were systematically reviewed from the epidemiologic perspective. PubMed was searched for studies examining hepatic fibrosis, cirrhosis, decompensated liver disease, hepatocellular carcinoma and liver-related death. Thirty-nine reports describing 34 unique studies met inclusion criteria. Information was abstracted on study design, sampling, frame, inclusion/exclusion criteria, sample size, results and covariates used for adjustment.

Because of the heterogeneity among study designs, a meta-analysis was not conducted.

Nine of the twelve cross-sectional studies showed a statistically significant association between HIV coinfection and fibrosis or cirrhosis, whereas seven retrospective cohort studies were inconsistent. Six studies examined decompensated liver disease as the outcome, five of these found significant increased risk in patients with HIV coinfection.

(continued on page 60)

(continued from page 58)

The seven studies examining liver-related deaths showed a trend toward association with HIV co-infection, although only four were statistically significant. Four studies examined the effect of HIV on hepatocellular carcinoma, two of which found no association. Of ten studies that were investigated, the effect of ART on the risk of liver disease, half reported a significant protective association.

It was concluded that HIV coinfection was associated with an increased risk of advanced liver disease in HCV-infected patients. Data on hepatocellular carcinoma are sparse, but an association is plausible, given the increased risk of advanced liver disease. In contrast, data for an effect of ART are plentiful, but findings are inconsistent. More robust studies are needed on that topic. (Kramer, J.R., Giordano, T.P., El-Serag, H.B. "Effect of Human Immunodeficiency Virus and Antiretrovirals on Outcomes of Hepatitis C: A Systematic Review from an Epidemiologic Perspective." *Clin Gastroenterol Hepatol*, 2007; Vol. 5, pp. 1321-1328.)

Risk of Pancreatitis in Celiac Disease

Fourteen thousand, two hundred and thirty-nine individuals with a diagnosis of celiac disease (CD) from 1964 to 2003, and 69,381 reference individuals matched for age, sex, calendar year and county of residence at the time of diagnosis was carried out. Cox regression estimated the hazard ratios (HRs) for subsequent diagnosis of pancreatitis. Analyses were restricted to individuals with more than one year of follow-up and no diagnosis of pancreatitis before or at one year after study entry. Conditional logistic regression estimated the association of pancreatitis with subsequent CD.

CD was associated with an increased risk of subsequent pancreatitis of any type (HR 3.3) and chronic pancreatitis (HR 19.8). Adjustment for socioeconomic index, diabetes mellitus, alcohol-related disorders or gallstone disease had no notable effect on the risk estimates. The risk increase for pancreatitis was only found among individuals with CD diagnosed in adulthood.

Pancreatitis of any type (odds ratio 3.2), and chronic pancreatitis (odds ratio 7.3), were associated with subsequent CD. The study suggested that individuals with CD are at increased risk for pancreatitis. (Ludvigsson, J.F., Montgomery, S.M., Ekblom, A. "Risk of Pancreati-

tis in 14,000 Individuals With Celiac Disease." *Clin Gastroenterol Hepatol*, 2007; Vol. 5, pp. 1347-1353.)

Entecavir Therapy in Chronic Hepatitis B

Entecavir demonstrated superior benefit to Lamivudine at 48 weeks in nucleoside-naïve patients with hepatitis Be antigen (HBeAg-positive chronic hepatitis B—CHB). Continued Entecavir and Lamivudine treatment through 96 weeks was evaluated.

Seven hundred nine HBeAg-positive CHB patients were randomized to Entecavir 0.5 mg (N = 354), or Lamivudine 100 mg (N = 355) once daily. At week 52, protocol-defined virologic responders could continue blinded treatment for up to 96 weeks. Patients continuing in year two on Entecavir (N = 243), Lamivudine (N = 164), were assessed for serum hepatitis B virus (HBV) DNA, ALT normalization, HBeAg seroconversion and safety. Cumulative confirmed portions of all treated patients who achieved these responses were also analyzed.

Among patients treated in year 2, 74% of Entecavir-treated versus 37% of Lamivudine-treated patients achieved HBV DNA less than 300 copies/mL by PCR and 79% of Entecavir-treated versus 68% of Lamivudine-treated patients normalized ALT levels. Similar proportions of Entecavir-treated and Lamivudine-treated patients achieved HBeAg seroconversion (11% versus 12%, respectively). Higher proportions of Entecavir-treated than Lamivudine-treated patients achieved cumulative confirmed HBV DNA less than 300 copies/mL by PCR (80% versus 39%) and ALT normalization (87% versus 79%) through 96 weeks.

Cumulative confirmed HBeAg seroconversion occurred in 31% of Entecavir versus 25% of Lamivudine-treated patients. Through 96 weeks, no patient experienced virologic breakthrough due to Entecavir resistance. The safety profile was comparable in both groups.

It was concluded that Entecavir treatment through 96 weeks resulted in continued benefit for patients with HBeAg-positive CHB. (Gish, R.G., Lok, A.S., Chang, P.T., et al. "Entecavir Therapy for up to 96 Weeks in Patients With HBeAg-Positive Chronic Hepatitis B." *Gastroenterology*, 2007; Vol. 133, pp. 1437-1440.)

Murray H. Cohen, D.O., editor of "From the Literature" is a member of the Editorial Board of *Practical Gastroenterology*.