

*27th Annual Report*

Digestive Diseases  
Interagency  
Coordinating Committee

Fiscal Year 2004

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Stephen P. James, MD  
*Chairperson*

# Digestive Diseases Interagency Coordinating Committee

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## *Executive Summary*

Section 440A of Public Law 94-562 in 1976 created the Digestive Diseases Coordinating Committee (DDCC) for the purpose of coordinating the digestive disease-related research activities of relevant Federal health agencies into a coordinated program aimed at combating digestive diseases. In 1986, Section 429 of Public Law 99-158 reauthorized the Digestive Diseases Interagency Coordinating Committee (DDICC) and created two new coordinating committees in diabetes mellitus and in kidney, urologic, and hematologic diseases under the auspices of the National Institute of Diabetes and Digestive and Kidney Diseases. In compliance with these laws, the DDICC has been functioning since 1976 to organize the efforts of relevant Federal health agencies into a coordinated program aimed at combating digestive diseases.

In holding three meetings in FY2004, the DDICC coordinated Federal efforts to combat digestive diseases via information exchange and facilitated cooperation and collaboration among the participating units.

Among the provisions governing coordinating committees is a requirement for an annual report to the Secretary of Health and Human Services, the Director of the National Institutes of Health, and to the Director, National Institute of Diabetes, Digestive and Kidney Diseases, established for the particular group of diseases.

This Twenty-seventh Annual Report summarizes the activities of the DDICC in Fiscal Year 2004 and the three meetings held by the DDICC in pursuit of its legislative mandate, as well as the membership of the DDICC. The initiatives of the DDICC members encompass a wide spectrum of digestive diseases-related activities, from the training of future researchers in digestive diseases to clinical research on specific diseases to basic research on the underlying mechanisms of disease processes.

## Digestive Diseases, the Health Problem

The numerous disorders known collectively as digestive diseases include serious and potentially life-threatening illnesses, such as cirrhosis of the liver, inflammatory bowel disease, hepatitis, cancer, ulcers, and gallstones and well as more frequent, but less serious illnesses such as acute gastroenteritis, gastroesophageal reflux disease (GERD) and irritable bowel syndrome (IBS). These acute and chronic disorders have the common element of affecting the digestive tract, which includes the pharynx, esophagus, stomach, liver, biliary tract, pancreas, small and large intestines, and anorectum.

Digestive diseases and their associated long-term complications have catastrophic social and economic consequences. According to a report in 2002, the most prevalent diseases were non-food-borne gastroenteritis (135 million cases/year), food-borne illness (76 million), gastroesophageal reflux disease (GERD; 19 million), and irritable bowel syndrome (IBS; 15 million). The disease with the highest annual direct costs in the United States was GERD (\$9.3 billion), followed by gallbladder disease (\$5.8 billion), colorectal cancer (\$4.8 billion), and peptic ulcer disease (\$3.1 billion). The estimated direct costs for these 17 diseases in 1998 dollars were \$36.0 billion, with estimated indirect costs of \$22.8 billion. The estimated direct costs for all digestive diseases were \$85.5 billion. The chronic nature of these diseases results in approximately 11 percent of all admissions to general hospitals in the United States and for 15 percent of all surgical procedures performed in this country. Approximately 200,000 deaths annually are caused by digestive diseases, including cirrhosis and other liver diseases, cancer of the digestive system, gallbladder disease, ulcers, and pancreatitis. Digestive diseases also complicate the treatment of other life-threatening conditions, such as cardiovascular disease.

Digestive diseases rank second among all causes of disability due to illness in the United States. They result in an estimated 200,000 absences from work each day with a mean time lost of 9 days. Digestive diseases are the leading cause of lost time from work for male employees. More than 2 million Americans are impaired to some degree by digestive diseases, limiting an estimated 1.2 million people in the type of occupation they can seek. Approximately 140,000 veterans receive payments for service-related disabilities due to digestive diseases.

## **The Digestive Diseases Interagency Coordinating Committee (DDICC)**

The DDICC promotes information acquisition and exchange, as well as facilitates cooperation and collaboration among relevant Federal health agencies to provide a coordinated effort to combat digestive diseases. The Committee met three times to encourage exchange of information among member organizations. It continued its role as a lead source of information on government-wide activities and support of digestive diseases research for other concerned governmental and non-governmental individuals and groups.

### **Meetings Held by the DDICC**

Each meeting provided the opportunity for members to report all upcoming Program Announcements (PA), Requests for Applications (RFA), and meetings involving digestive disease topics. In addition, invited speaker(s) provide a current topical update on basic and clinical investigations to the members of the DDICC. The update serves as a focus to provide an opportunity for members to highlight their organization's activities and grant support for the specific topic under discussion.

## **Meeting of the Liver Disease Subcommittee of the Digestive Diseases Interagency Coordinating Committee on Approaches to the Development of an NIH Action Plan for Liver Disease Research**

November 25, 2003

Conference Room 6, Building 31

NIH Campus

Bethesda, Maryland

### **SESSION ONE: CURRENT BURDEN OF LIVER DISEASE IN THE U.S.**

#### ***Welcome and Introduction***

Dr. Allen M. Spiegel, Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)

In 2003, in response to congressional and lay interest, the NIDDK created the Liver Disease Research Branch within the Division of Digestive Diseases and Nutrition (DDDN) and appointed Dr. Jay Hoofnagle as its founding Director. The purpose of creating a new Branch was to bring greater visibility and focus to liver disease and to ensure growth and excellence in NIH-funded liver-related research. The new Branch will help to enhance research on critical areas, such as basic research on the liver; viral hepatitis B and C; alcoholic and nonalcoholic fatty liver disease; autoimmune, genetic and pediatric liver diseases; biliary and gallbladder disorders; liver transplantation; and complications of end-stage liver disease.

As an initial and defining task, the new Liver Disease Research Branch was charged with developing an Action Plan for Liver Disease Research. This Action Plan was to be developed in coordination with all elements of the NIH involved with liver disease-related research. The Branch was specifically charged with working

together with other Institutes and Centers on liver disease research, including the National Cancer Institute (NCI) in studies on liver cancer; the National Institute of Allergy and Infectious Diseases (NIAID) on studies of viral hepatitis and autoimmunity; the National Institute on Drug Abuse (NIDA) in studies on viral hepatitis among injection drug users; the National Institute of Child Health and Human Development (NICHD) in studies on liver development and maternal and pediatric liver disease; the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in studies on alcoholic liver disease; the National Institute of Environmental Health Sciences (NIEHS) on drug- and toxicant- induced liver disease; and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) in studies on liver imaging and biotechnology and the liver.

To accomplish these objectives of trans-NIH coordination and development of an Action Plan, the LDR Branch was also directed to establish a Liver Disease Subcommittee (LDS) of the statutory Digestive Diseases Interagency Coordinating Committee (DDICC), which the NIDDK chairs. This meeting of the Liver Disease Subcommittee was called to initiate work on the Action Plan for Liver Disease Research and begin the important task of trans-NIH coordination in liver disease related research funding.

### ***Vital Statistics and Liver Disease in the United States***

Dr. Jay H. Hoofnagle, Director, Liver Disease Research Branch, NIDDK, NIH, and Chair, Liver Disease Subcommittee, DDICC.

Acute and chronic liver diseases are important causes of morbidity and mortality in the U. S. Data on mortality of chronic liver disease in the U.S. derives mainly from death reports and vital statistics from the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC). In 2001, there were 27,305 deaths from chronic liver disease and cirrhosis (ICD codes: 571.0-571.9) thus accounting for 1.1 percent of all deaths and ranking as the twelfth major cause of death. The age-adjusted rate of death for chronic liver disease and cirrhosis was 9.5/100,000 population, the lowest rate in U.S. history. Such data suggest that liver disease death rates are falling.

The difficulties with interpretation of data from vital statistics, however, are many, including inaccuracy of death records, under-reporting of liver disease, coding artifacts and the overall increasing age of the population. Thus, the code for chronic liver disease and cirrhosis may not be used for patients with chronic hepatitis B or C, which may be coded instead as "viral hepatitis" (070.2-070.9). Furthermore, hepatocellular carcinoma (HCC) is an important complication and common cause of death in patients with chronic liver diseases, but is counted separately in death statistics (ICD code C22). When these several codes are combined, liver disease accounts for approximately 46,000 deaths yearly (1.9 percent of deaths) and ranks ninth in overall causes of death.

Importantly, while deaths from cirrhosis have decreased in frequency, the incidence of liver cancer is on the rise, and the major cause for this increase appears to be hepatitis C. Thus, antibody to hepatitis C virus (anti-HCV) is found in over half of patients with HCC and data from hospitalizations as well as the SEERS database have suggested that the incidence of HCC has doubled (1.4 to 3.0 per 100,000 population) in the last 25 years. HCC also now accounts for almost one-quarter of liver transplants done in the U.S. in adults each year.

Another important factor in liver disease is the age-specific and racial/ethnic differences in death rates. Thus, the average mortality rate for chronic liver disease and cirrhosis increases with age, but only to 65 years, after which rates level off and decline. As a consequence, the relative rates of death from liver disease are higher during young and middle adulthood. Chronic liver disease/cirrhosis is the fourth leading cause of death for persons between the ages of 45 to 54 years, and the seventh leading cause of death for those 35 to 44 and 55 to 64. Furthermore, there are racial differences in death rates from chronic liver disease and cirrhosis. Thus, among non-Hispanic whites and African Americans, this diagnosis ranks twelfth as a cause of death and death rates are 9.5 per 100,000 population. In contrast, among Hispanic whites, these diagnoses rank seventh as cause of death and among American Indians, they rank sixth. Indeed, in American Indian males between the ages of 35 and 44, cirrhosis is the second most common cause of death. Reasons for these racial differences have not been well defined.

### ***Chronic Liver Disease in the United States***

Dr. Beth P. Bell, Division of Viral Hepatitis, National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC)

There are no comprehensive, population-based assessments of the current burden of liver disease in the U.S. population. Because of the inaccuracies of diagnoses on death certificates and the underreporting of liver disease, reported mortality rates from chronic liver disease are likely to be underestimated. Furthermore, death records rarely provide information on specific etiology of chronic liver disease or cirrhosis and do not provide information on the morbidity of liver disease. For these reasons, the CDC, in collaboration with NIDDK, has established a chronic liver disease surveillance program that is currently active in three U.S. counties: New Haven, Connecticut; Alameda (Oakland), California; and Multnomah (Portland), Oregon. The surveillance system provides information on all newly diagnosed cases of chronic liver disease in gastroenterologists' offices, and uses standardized approaches to clinical and laboratory diagnosis and validated instruments to assess lifetime alcohol use and risk factors for viral hepatitis and other liver diseases. Preliminary analysis of the initial 725 patients enrolled indicated that the etiology of these patients' chronic liver disease included: chronic hepatitis C, 42 percent; hepatitis C and excessive alcohol intake, 22 percent; excessive alcohol intake, 8 percent; nonalcoholic fatty liver disease, 10 percent; chronic hepatitis B, 4 percent; and miscellaneous other liver conditions (including autoimmune hepatitis, drug-induced liver disease, hemochromatosis, primary biliary cirrhosis, sclerosing cholangitis, HCC, and granulomatous liver disease), 8 percent. There were insufficient data to characterize the etiology in the

remaining 6 percent of patients. Based upon these results, it is estimated that the incidence of newly diagnosed chronic liver disease in referral practices is 67 per 100,000 in the population, and that 150,000 new cases of chronic liver disease are diagnosed in gastroenterologists' offices yearly in the U.S. Approximately two-thirds of diagnosed cases have hepatitis C, and 20 percent already have cirrhosis at the time of initial diagnosis. Some diagnoses may be under-represented in these surveillance studies, particularly NASH and alcoholic liver disease, largely because these patients may not be referred to specialists for evaluation.

As a part of this surveillance system, a death certificate validation study was performed in two of the surveillance counties. Comparison of death certificates and medical charts of patients dying with the diagnosis of liver disease demonstrated inaccuracies in coding for cirrhosis and liver disease and their etiologies on the death certificates. These analyses suggested that the overall mortality burden of chronic liver disease is likely to be as much as 30 percent higher than indicated by routine analysis of death certificates, and that both hepatitis C and alcoholic liver disease are underreported on death certificates.

### ***Liver Transplantation in the United States***

Dr. Michael R. Lucey, University of Wisconsin-Madison Medical School

Liver transplantation is now considered standard therapy for patients with end-stage liver disease, regardless of diagnosis. At present, approximately 5,000 liver transplants are done yearly in the U.S. at more than 120 medical centers. The number of liver

transplants, however, is limited by the availability of organs. Thus, while the number of transplants performed in the U.S. has steadily increased over the last twenty years, the number of persons needing liver transplant has increased even more rapidly. As a consequence, the waiting list for liver transplantation has steadily risen; currently, there are more than 17,000 persons on the liver transplant waiting list and at least 1,500 will die annually while waiting.

Discrepancies in criteria for listing for transplantation and in waiting list mortality across the U. S. led to attempts to standardize listing criteria and to the adoption of the Model for End-Stage Liver Disease (MELD) score as a standardized and objective means of evaluating the severity of illness and likelihood of death from liver disease. MELD scores were developed to accurately reflect three-month mortality estimates in patients with chronic liver disease. The MELD is a continuous score ranging from 0 to over 40 and is derived from values for serum bilirubin, prothrombin time (INR), and creatinine. Use of the MELD score minimizes time on the waiting list as a criterion for transplantation and avoids subjectivity in the assessment of the need for transplant. Persons with HCC who are otherwise eligible for transplantation are given a MELD score of either 20 or 24, which increases their chances of timely transplantation. Since the introduction of the MELD system in 2002, the numbers of persons on the waiting list has decreased, and deaths on the waiting list have stabilized or decreased slightly.

According to the UNOS database, which incorporates more than 15 years of liver transplantation, survival after liver transplantation averages 80 percent at one year and more than 60 percent at 5 years. Recent data would suggest that current

graft and patient survival rates have improved further. An exception to these data is liver transplantation for HCC, for which five-year survival in the UNOS database is less than 40 percent. The issue of poor survival in patients with HCC is of particular concern, because it is an increasing reason for transplantation, and its incidence is rising in the U.S. as the age of patients at presentation is falling. Small series suggest that patient and graft survival in patients with HCC is improved when careful selection protocols are used. The changes in prioritization of candidates using the MELD scoring system discussed have had the effect that, at present, almost one-quarter of liver transplants in the U.S. are done in patients with HCC.

The challenges in liver transplantation are many. The demand for liver transplantation is likely to continue to rise, and a central problem is the shortage of donor livers. Several approaches have been taken to help alleviate this problem, the most practical at present being use of living donor liver transplantation, which now accounts for approximately 5 percent of transplants done in adults and one-third of those done in children. Other research approaches are as yet not clinically practical, but are the focus of much research; these include use of artificial organs, hepatocyte transplantation, and xenotransplantation.

A second major clinical and research issue in liver transplantation is immunosuppression. Immunosuppressive regimens have improved greatly in the last 20 years, but one-half of all liver transplant recipients experience at least one episode of acute rejection. Chronic rejection can result in graft loss, and infectious complications of immunosuppression are a major cause of death after transplantation. Moreover, many of

the long-term morbidities associated with liver transplantation, such as hypertension, diabetes mellitus, renal failure, hyperlipidemia, cardiovascular disease and gout, are the direct consequence of chronic use of immunosuppressant agents. A better understanding of tolerance and means of withdrawal of immunosuppression after transplantation, which is possible in some patients, is of central importance in improving this approach to reversal of end-stage liver disease.

A final important clinical and research issue in liver transplantation is the problem of recurrence of disease. A common limitation of the long-term success of liver transplants is recurrence of the primary disease, such as hepatitis C or B, nonalcoholic fatty liver disease (also called nonalcoholic steatohepatitis or NASH), alcoholic liver disease, and autoimmune liver conditions, such as primary biliary cirrhosis, sclerosing cholangitis, and autoimmune hepatitis. Research is needed on how to prevent or ameliorate the course of these diseases after transplantation.

### ***Liver Disease in the HIV-Positive Patient***

Dr. David Thomas, Professor of Medicine,  
Division of Infectious Diseases,  
The Johns Hopkins School of Medicine

Liver disease is becoming an increasingly important problem in HIV-infected patients. The causes of liver disease in this population are many, and include hepatitis B and C, NASH, alcoholic liver disease, drug-induced liver disease, and opportunistic infections of the liver and biliary tree (e.g., atypical mycobacterium, cryptosporidiosis, cytomegalovirus)

as well as immunodeficiency-associated cancers (lymphoma). Since the advent of highly active anti-retroviral therapy (HAART) in 1996, the incidence of opportunistic liver infections has diminished sharply, as has HIV-related mortality. In contrast, viral hepatitis-related morbidity and mortality has increased, and it is now one of the leading causes of death among HIV-infected persons in many settings.

One in four patients with HIV in the U.S. (approximately 200,000 individuals) is seropositive for anti-HCV, indicating previous or ongoing infection. The prevalence of HCV infection is highest (50 to 90 percent) among persons who acquired HIV infection from injection drug use. HCV infection is adversely affected by co-infection with HIV at every stage of its natural history; the proportion of patients who recover is much lower; and the disease progresses from persistent infection to cirrhosis to end-stage liver disease (ESLD) more rapidly. HAART for HIV infection, while effective in prolonging survival, may ultimately increase the mortality rate from ESLD. Patients with HCV are at an increased risk for liver injury from anti-retroviral therapy. In addition, approximately 10 percent of patients with HIV infection are co-infected with hepatitis B and the incidence of cirrhosis also is increased in this group.

The biologic mechanisms for the clinical interactions between HIV, HBV, and HCV are not known. Important areas for future research include the pathogenesis of liver diseases; fibrosis progression rates; treatment regimens; outcomes and duration; liver transplantation (for HIV-positive individuals with ESLD); and treatment access (e.g., how to access difficult-to-reach populations).

### ***Action Plan for Liver Disease Research***

Dr. Jay H. Hoofnagle, Director, Liver Disease Research Branch, NIDDK, NIH, and Chair, Liver Disease Subcommittee, DDICC.

In addressing the enormous health burden of liver diseases, the new Liver Disease Subcommittee (LDS) of the statutory Digestive Diseases Interagency Coordinating Committee will promote the coordination of activities among different NIH components and other Federal agencies in liver disease research. An initial charge to the Liver Disease Subcommittee is to develop an Action Plan for liver disease research, and monitor its implementation.

It is envisioned that the Action Plan for Liver Disease Research would have the following topic areas:

- Cell and molecular biology of liver
  - Hepatocyte biology
  - Cell injury, repair, inflammation and fibrosis
  - Developmental biology and liver regeneration
  - Bile, bile acids and cholestasis
- Viral hepatitis and infectious diseases of the liver
- HIV and liver disease
- Fatty liver disease
- Drug- and toxicant-induced liver injury
- Autoimmune liver disease
- Pediatric liver disease
- Genetic liver disease
- Liver transplantation
- Complications of chronic liver disease
- Liver cancer
- Gallbladder and biliary disease
- Bioengineering and biotechnology

To aid in the development of the Action Plan, the Liver Disease Subcommittee will invite experts in each of these topic areas to serve on working groups that can assist in developing background information and narrative. These working groups will be primarily composed of external scientific and lay leaders in the liver disease community. Input on membership is solicited from the Liver Disease Subcommittee members and all participants in the meeting.

### **SESSION TWO NIH FUNDING IN LIVER DISEASE**

#### ***Overview of NIH funding in Liver Disease***

Dr. Jay H. Hoofnagle, Director, Liver Disease Research Branch, NIDDK, NIH, and Chair, Liver Disease Subcommittee, DDICC.

Overall NIH funding in liver disease research for FY 2003 was an estimated \$378 million which represents a 3-fold growth since 1993 (\$123.8 million). Importantly, from 1998 to 2003, while the NIH budget doubled, funding for liver disease research increased by 110 percent (from \$180 million to an estimated \$378 million). Thus, the rate of growth in liver disease research funding has been vigorous and commensurate with that of the NIH overall.

Complete information is available on specific grants and awards and budget reported for FY 2002. In that year, 16 NIH Institutes and Centers reported making over 1,600 awards for liver disease research, using a wide variety of funding mechanisms, for a total expenditure of \$348.5 million. The Institutes with the major proportion of liver disease related research funding included the NIDDK (\$137.9 million, 40 percent), NCI (\$62.5 million, 18 percent),

NIAID (\$56.7 million, 18 percent), NIAAA (\$29.7 million, 9 percent), and NIEHS (\$21.8 million, 6 percent).

As a part of development of an Action Plan, the grants in the entire portfolio of liver disease research for FY 2002 were classified into one of the 12 categories of liver research defined as the topic areas for the Action Plan. Grants were coded informally, largely on the basis of the title and funding source. A single code was used to categorize grants, even though many grants dealt with more than one of the topic areas. Despite these shortcomings, the analysis provided an overview of the current levels of funding in these different areas. The major areas of funding were in basic research (233 awards for \$71 million), viral hepatitis (452 awards for \$114.8 million), and liver cancer (429 awards for \$53.8 million). Fatty liver disease (123 awards, \$31 million) and drug- and toxicant-induced liver injury (110 awards, \$25 million) also received extensive funding. Funding for viral hepatitis research was shared among several institutes: NIAID, NCI, NIDDK, NIAAA, NIDA, NHLBI, and NCCR. The majority of grants were funded in liver cancer by NCI, in fatty liver disease by NIAAA, and in drug- and toxicant-induced liver injury by NIEHS. NIDDK funded the majority, but not all, of research on pediatric liver disease (59 awards, \$11 million), genetic liver disease (61 awards, \$15.5 million), liver transplantation (49 awards, \$9.1 million), complications of cirrhosis (41 awards, \$7.8 million), and gallstones (11 awards, \$2 million). In FY 2002, viral hepatitis was the subject of the most NIH grants in liver disease research. The 452 grants, awards, contracts, fellowships, career awards, and NIH intramural projects included 39 on hepatitis B, 279 on hepatitis C, and 25 on HIV and the liver.

### ***National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)***

Dr. Jose Serrano, Director for Liver and Biliary Program, Liver Disease Research Branch

In FY 2002, the NIDDK supported 393 research projects on liver disease for a total expenditure of \$136.8 million. Of these projects, 128 were clinical research and 265 were basic research (119 liver disease projects and 146 liver function/structure projects). Liver research is supported across the NIDDK extramural divisions and the Intramural Research Program. In the area of basic research, studies in cell and molecular biology received the most NIDDK support. Major mechanisms of support for basic research include typical investigator-initiated research project grants (R01s), exploratory grants (R21s), program projects (P01s), and core center grants (P30s). Clinical and translational research is encouraged and supported through typical R01s as well as small clinical grants (R03s) and cooperative agreements (U01s). At present, NIDDK supports clinical studies in chronic hepatitis B and C, NASH, primary biliary cirrhosis, sclerosing cholangitis, biliary atresia, alpha-1-antitrypsin deficiency, acute liver failure, managements of esophageal varices and ascites, drug-induced liver disease, and liver transplantation.

Many of the current initiatives supported by NIDDK in liver disease research are trans-NIH, involving close collaborations with other Institutes and Centers. Future initiatives for FY 2004 and 2005 will address topics such as the liver proteome, autoimmune hepatitis, silymarin and SAME for chronic liver disease, and hepatocellular carcinoma. The following meetings are planned:

- Silymarin and Chronic Liver Diseases, March 22, 2004
- Hepatocellular Carcinoma, April 1B3, 2004
- Interferon: HCV: Liver: Molecular studies of interactions, Fall 2004
- Primary sclerosing cholangitis, Fall 2004
- Liver Disease in Native Americans, Winter 2004

### ***National Institute of Allergy and Infectious Diseases (NIAID)***

Dr. Leslye Johnson, Chief, Enteric and Hepatic Diseases Branch

In FY 2001, NIAID supported 201 grants and awards in liver disease research for a total budget of \$56.7 million. These included studies of all five hepatitis viruses, HIV coinfection, schistosomiasis, malaria, and *Entamoeba histolytica*. NIAID also funds a large number of studies of general autoimmunity, some of which focus on an infectious cause of primary biliary cirrhosis and autoimmune hepatitis. Liver disease research at the NIAID spans a continuum from basic research to clinical applications. A major focus of activity is the development of vaccines, therapies, and diagnostics for infectious diseases of the liver. Early-stage research focuses on pathogen biology (e.g., replication) and host response (e.g., immune pathogenesis, evasion, and protective response), and includes work in vitro and in vivo—both in animal models and humans. Such efforts often identify possible therapeutic targets and potential interventions. Basic research efforts include support for Hepatitis C Cooperative Research Centers; studies of the complications of HIV infection; and investigations of viral replication processes, immunopathogenesis of viral hepatitis, complexities of the immune response

during infection of the liver, and aspects of tropical diseases that affect the liver. Significant emphasis is placed on translational research for the application of basic science results in clinical situations. These efforts include an in vitro antiviral screening program for agents with antiviral activity against HBV and HCV; use of animal models for evaluation of candidate therapies for HBV; and partnership grants for novel hepatitis B therapies. With respect to clinical evaluation, the NIAID supports collaborative contracts that primarily focus on phase I and II clinical trials. These research partnerships include a collaborative antiviral studies group; vaccine and treatment evaluation units; and adult AIDS clinical trial units. Complementing these contracts are grants for cooperative agreements and Small Business Innovation Research. Several valuable research resources underpin NIAID's efforts, including the HCV sequence database at Los Alamos National Laboratory, a research and reference reagent program, and a tetramer facility.

### ***National Cancer Institute (NCI)***

Dr. Jaye L. Viner, Gastrointestinal and Other Cancers Research Group Division of Cancer Prevention

In FY 2002, the NCI funded 451 awards in liver disease research for a total budget of \$62.5 million. These awards represent NCI-funded grants focused largely on primary hepatocellular carcinoma (HCC), but also include studies of cancers of the liver and biliary tree, such as cholangiocarcinoma, hepatoblastoma, angiosarcoma, and lymphoma. Primary HCC is one of the most prevalent cancers worldwide, accounting for an estimated 500,000 deaths yearly, and HCC rates in the U.S. have risen sharply

over recent years. The NCI's SEER cancer database documents a 2-fold increase in HCC incidence in the U.S. (1.4/100,000 cases in 1976-1980 versus 3.0/100,000 cases in 1996-1998). HCC-related mortality also increased during this period, as expected for a disease lacking effective medical interventions and that is typically diagnosed at surgically incurable stages. Recent epidemiologic trends and global experience-in particular, rising HCC rates linked to hepatitis C viral spread-predict for an increasing burden of HCC in the U.S. population. Certain risk factors for HCC are modifiable or preventable (e.g., alcohol consumption and diet, standard precautions against blood borne pathogens, and pre-exposure hepatitis B vaccination), and the long latency between exposure and the development of invasive disease potentially provides opportunities for disease intervention. The majority of NCI funding for liver cancer research was allocated to awards under the R01 research mechanism. NCI-funded clinical research largely involves small phase I and II trials to test anticancer agents. While the NCI has contributed significantly to the overall NIH HCC effort, inquiries into the infectious etiology of HCC and research interests of other ICs in liver diseases-including cancer-have been included in initiatives where other ICs have played a primary role. Research initiatives related to liver disease include the Clinical Trials Cooperative Group Program, Early Phase Trials Consortium, Early Detection Research Network, and co-funding of the HALT-C trial with NIDDK and NIAID. A GI Translational Research Network has been proposed to transcend the limits of the current system and translate basic science research to visible clinical results. The model represents a partnership among research priorities, foundational principles, and research products to improve patient care and public health.

### ***National Institute of Alcoholism and Alcohol Abuse (NIAAA)***

Dr. Sam Zakhari, Director, Division of Basic Research

In FY 2002 the NIAAA supported 107 liver disease research grants and awards for a total budget of \$29.7 million. NIAAA-funded research on liver disease is focused in many of the scientific areas selected as topic areas for the Action Plan, including cell and molecular biology of the liver; viral hepatitis; alcoholic fatty liver disease; drug- and toxicant-induced liver disease; genetic liver diseases; liver transplantation; and liver cancer. Areas of special interest to the Institute include preclinical studies on medications for alcoholic liver disease, such as silymarin and SAME; the role of alcohol in the course and complications of chronic hepatitis C; and treatments for hepatic encephalopathy.

The NIAAA funds considerable research on the metabolism of alcohol, which in the liver is metabolized to acetaldehyde (by alcohol dehydrogenase and CYP 2E1) and from acetaldehyde to acetate. Aspects of these studies include issues related to molecular biology, gene expression, hormone action, enzyme kinetics and structure, and ethnic/genetic differences. Also of research interest are studies of the mechanisms of cell injury in the liver, including free radicals and cytokines, and the role of alcohol in promoting the development of fibrosis. At present, a major initiative by NIAAA is in the area of pathogenesis of fatty liver disease.

### ***National Institute of Environmental Health Sciences (NIEHS)***

Dr. Carol Shreffler, Health Science Administrator, Cellular, Organ and Systems Pathobiology Branch, Division of Extramural Research and Training

For FY 2002, NIEHS funded 85 awards in liver disease-related research for a total budget of \$21.8 million, largely in the topic area of drug- and toxicant-induced liver disease and metabolism of chemicals and drugs by the liver. The mission of the NIEHS is to reduce the burden of diseases and dysfunctions associated with the environment (e.g., exposure to chemical and physical agents), with a focus on mechanistic studies and public health interventions. The NIEHS supports studies of drug and toxicant metabolism and the liver, as well as the pathology and epidemiology of liver cancer. Types of liver injury that have been associated with chemicals include fatty liver, liver-cell death, canalicular cholestasis, bile duct damage, cirrhosis, vascular disorders, and tumors. Over 140 chemicals have been identified with neoplasia in the liver. The National Toxicology Program of NIEHS supports intramural research and contracts for toxicological testing programs, development of testing methods, and reporting of toxicity data. Goals of the National Center for Toxicogenomics include: evaluation of toxicant-specific patterns of gene expression using microarray technology; identification of biomarkers of disease and exposure; improvement of computational methods, and creation of a public database of environmental effects of toxic substances on biological systems. The Toxicogenomics Research Consortium was formed to identify and characterize sources of variation in gene expression experiments and to establish standard protocols ("Abest practices"). Through these and other efforts, the NIEHS is contributing

important knowledge about animal toxicity, which can be translated by other organizations into studies of the clinical pharmacology of toxic agents and human liver disease.

### **SESSION THREE**

#### **ACTION PLAN FOR LIVER DISEASE RESEARCH**

##### ***Introduction and Overview***

Dr. Jay H. Hoofnagle, Director, Liver Disease Research Branch, NIDDK, NIH, and Chair, Liver Disease Subcommittee, DDICC.

The goal of the Action Plan is to advance research on liver disease in order to decrease the burden of liver disease in the United States. The Action Plan will include an overview of the current status of liver disease research, 13 to 16 chapters covering the separate focus areas (described previously), major goals for liver research, steps needed to reach these major goals, and means of assessing progress. The Action Plan will be directed at the NIH and the research mechanisms it uses to support its mission. It should be sufficiently flexible to serve as a scientific guidepost over the next five to ten years, independent of funding levels. It should also be compatible with other NIH initiatives, and emphasize a common theme of translation of basic research into practical means for the management and prevention of disease. It is expected that the Action Plan will be completed in 2004.

Five principles will guide development under the Action Plan for Liver Disease Research.

- Stress basic research.
- Strive to rapidly translate findings from basic research to practical means of prevention, control, and cure of liver diseases.

- Ensure that the clinical advances made in research are disseminated to the medical community and patients with liver disease.
- Use all mechanisms and sources for support of research and promote cooperation and coordination.
- Emphasize training and career development in research on liver diseases.

The Action Plan will be the result of a wide consensus of opinions and input from all groups involved in liver disease research as well as concerned and committed lay organizations and persons with liver disease. Initial draft language for the Action Plan will be developed by working groups who will be selected by the Liver Disease Subcommittee for each of the 13-16 topic areas. The working groups will include NIH-funded investigators (extramural and intramural) in the topic areas and will solicit advice and input from other groups and concerned individuals both by direct contacts and through outreach using the internet.

A web site ([http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb\\_action\\_plan.htm](http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb_action_plan.htm)) will offer an overview of the Action Plan; an outline of the research topic areas; recent developments; hand-outs, minutes, and other relevant communications; current data on the burden of liver disease; and information on the status of research funding. The NIDDK will update this information, as appropriate. In addition, investigators and lay persons interested in promoting liver disease research will be encouraged to visit the site and submit comments which will be shared with the working groups. The Action Plan will also be described in scientific publications (*Hepatology* 2003; 38:1348), and further input will be requested by direct e-mails to liver disease research investigators.

### Public Comment

Representatives from multiple academic and lay organizations were asked to participate in this meeting and to become engaged in the process for developing the Action Plan. Comments were solicited from all participants. The following comments were made, encouraging that consideration be given to or emphasis placed on:

- Alternative ways for optimal integration of basic research into the organizational framework for the Action Plan.
- Speeding the translation of new genetic insights gained from the Human Genome Project into clinical research on liver diseases, which will subsequently lead to improvements in human health.
- Epidemiologic research, including better surveillance, as a critically important foundation for hypothesis-driven research.
- Communicating the public health burden and implications of liver diseases as a compelling reason for intensifying research programs.
- Need for more effective information and education programs for liver disease patients and their health care providers.
- Research imperatives surrounding co-infection with HIV and HCV, including decisions with respect to liver transplantation, and the screening of HIV-infected patients for HCV to help prevent acceleration of liver damage.
- Importance of addressing all forms of hepatitis in the research agenda.
- Research centers as mechanisms that can facilitate the pooling of resources from different ICs and contribute to the goals of translation in ways that may not be possible through the traditional R01 grant mechanism.
- Approaches for harnessing new technologies and bringing them to bear for answering questions in liver disease research.

- Identification of research barriers and ways in which they can be removed or mitigated.
- Thinking in new and revolutionary ways rather than conventional terms in order to meet research challenges and solve problems.
- Developing both short-term and long-range research goals and objectives.
- Taking advantage of large-scale science initiatives, such as consortia, and especially, the NIH Roadmap process, which features cross-cutting research initiatives such as molecular libraries.
- Relationship of the Action Plan to future NIH-funding emphases on liver disease research.
- Involvement of all relevant NIH institutes and centers in development of the Action Plan.
- Leveraging public-private research partnerships in the fight against liver diseases.
- Collaborations with other Federal agencies.

The Action Plan will be formulated as a succinct and focused document outlining research goals and the opportunities and challenges in reaching these goals. Because the Plan is being developed by a Committee composed of Federal representatives, the recommendations of the Action Plan will be framed in scientific rather than budgetary terms. With respect to the incorporation of both short- and long-term goals, a recommended approach was the use of 3x3 matrices similar to those developed by the Office of the Director, NIH, for the description of goals under the Government Performance and Results Act (GPRA). These matrices are a means of displaying short-, medium- and long-range goals juxtaposed to degree of difficulty (low, medium and high risk) in achieving each. The final Action Plan will conclude with a “top ten” goals for liver disease

research and description of the challenges and opportunities in achieving these goals. These top ten goals will then provide a index for monitoring of the Action Plan for its completion and success. The meeting participants responded favorably to this approach. A timeline for developing the Action Plan was proposed.

### ***Timeline and Focus of Final Report***

- November 2003: Meeting of the Liver Disease Subcommittee to finalize design and initiate process of developing the Action Plan for Liver Disease Research
- December 1, 2003: Web site initiated
- January 2004: Selection of topic Working Groups
- February 2004: First draft of working groups
- February 2004: Liver Disease Subcommittee meeting
- March 2004: Second draft from working groups
- April 2004: Final draft submitted

### **ADJOURNMENT**

#### ***Appendix. Acronyms used in Minutes***

<b>CDC</b>	Centers for Disease Control and Prevention
<b>DDICC</b>	Digestive Diseases Interagency Coordinating Committee
<b>DDDN</b>	Division of Digestive Diseases and Nutrition
<b>ESLD</b>	end-stage liver disease

<b>HAART</b>	highly active anti-retroviral therapy	<b>NIAAA</b>	National Institute on Alcohol Abuse and Alcoholism
<b>HBV</b>	hepatitis B virus	<b>NIAID</b>	National Institute of Allergy and Infectious Diseases
<b>HCC</b>	hepatocellular carcinoma	<b>NIBIB</b>	National Institute of Biomedical Imaging and Bioengineering
<b>HCV</b>	hepatitis C virus	<b>NICHD</b>	National Institute of Child Health and Human Development
<b>HIV</b>	human immunodeficiency virus	<b>NIDA</b>	National Institute on Drug Abuse
<b>IC</b>	Institute or Center of the NIH	<b>NIDDK</b>	National Institute of Diabetes and Digestive and Kidney Diseases
<b>LDS</b>	Liver Disease Subcommittee	<b>NIEHS</b>	National Institute of Environmental Health Sciences
<b>MELD</b>	Model for End-stage Liver Disease	<b>NIH</b>	National Institutes of Health
<b>NASH</b>	nonalcoholic steatohepatitis	<b>UNOS</b>	United Network for Organ Sharing
<b>NCHS</b>	National Center for Health Statistics		
<b>NCI</b>	National Cancer Institute		
<b>NCRR</b>	National Center for Research Resources		
<b>NHLBI</b>	National Heart Lung and Blood Institute		

## Digestive Diseases Interagency Coordinating Committee

### Gastroparesis: A Common Disorder

April 2, 2004

Building 31C, Room 7C

National Institutes of Health Campus

Bethesda, Maryland

#### **Welcome & Opening Remarks**

Stephen P. James, M.D., Director, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, Bethesda, MD

Dr. James opened the meeting and asked participants to introduce themselves. Dr. Chung Owyang (Internal Medicine Department, University of Michigan, Ann Arbor, MI) thanked the meeting's organizers and stated that the objective of the meeting was to review and evaluate the current scientific information and research on gastroparesis throughout the NIH and other Federal agencies. The panel will identify deficiencies and gaps in knowledge in order to assist in the planning of future initiatives in gastroparesis. Dr. Owyang described gastroparesis as a very debilitating disorder, the pathogenesis of which is unclear and treatment options are limited. It is a common gastrointestinal problem afflicting approximately 5 million Americans, and which is therefore probably underfunded. Dr. Owyang outlined the structure of the agenda and the meeting, and introduced the first speaker, Dr. Henry Parkman.

#### **Overview of the Epidemiology, Clinical Aspects, Diagnosis and Economic Burden of Gastroparesis**

Henry Parkman, M.D., Department of Medicine, Temple University Hospital, Philadelphia, PA

Dr. Parkman offered a brief history of the disorder, stating that "gastroparesis" was initially used in the 1958 by P. Kassander to describe a condition called "gastroparesis diabeticorum," primarily applied to diabetics. The term has since been broadened to encompass a disorder of the stomach characterized by delayed gastric emptying without evidence of obstruction.

Diagnosis of gastroparesis is a three-step process. When a patient presents with symptoms suggestive of gastroparesis, clinicians must first use differential diagnoses, including ulcer, obstruction, cancer, functional dyspepsia, or psychological disorders (e.g., rumination syndrome or bulimia). Secondly, exclusion of organic lesions causing symptoms is done by means of an upper endoscopy (EGD) and upper gastrointestinal radiographic series (UGI). Gastroenterologists then evaluate evidence of

delayed gastric emptying. The gold standard is the scintigraphic emptying test of the solid phase; however, in the last decade, research indicates the <sup>13</sup>C-Octanoate Breath Test (OBT) might be useful as a simple screening test. Octanoic acid is absorbed, metabolized, and excreted in the liver. The carbon is tagged in the patient's ingested meal and measured in the breath sample. A comparison of OBT with gastric emptying scintigraphy reveals a fairly good correlation.

Dr. Parkman presented an example of a gastric emptying scintigraphy test which depicted normal gastric emptying at greater than 50% after 2 hours, and greater than 90% after 4 hours. Those results were compared to a patient with delayed gastric emptying who exhibited marked retention after 2 hours and only minimal emptying after 4 hours. (Dr. Parkman pointed out that research by a number of investigators has shown that the 2- and 4-hour times are probably the most useful in the diagnosis and differentiation of delayed gastric emptying from normal gastric emptying.)

Investigators can measure the rhythmicity of the stomach with an electrogastrogram (EGG). Dr. Parkman explained that, in normal stomach motility, a pacemaker along the greater curvature of the stomach emanates signals at 3 cycles per minute, generated probably in the Interstitial Cells of Cajal, which govern the peristalsis of the stomach. Three cycles per minute are added in fasting and also in the postprandial period, with an increase in electrical activity following ingestion. Dr. Parkman stated that although the EGG is a useful research tool, it is not currently employed in clinical evaluation of patients.

Dr. Parkman described a study conducted by Drs. Soykan and McCallum (DDS 1998;43:2398) which summarized the clinical characteristics of 146

patients with gastroparesis at tertiary motility centers. The majority of gastroparesis patients are middle-aged women (82%) with symptoms presenting at an average of 34 years of age. Symptoms include nausea, vomiting, bloating, early satiety, and abdominal pain/discomfort. The study also identified primary causes of gastroparesis as idiopathic (36%), although diabetic and post-surgical gastroparesis comprise 42% of patients affected by the disorder. Parkinson's disease, collagen vascular disorders, and intestinal pseudo-obstruction are rarer causes.

The prototype gastromotility disorder is probably diabetic gastroparesis, which Dr. Parkman stated is most often associated with long-standing insulin-dependent or Type 1 diabetes mellitus. In patients with long-standing duration, approximately 25 to 50% have been shown to have delayed gastric emptying, often occurring with other complications of diabetes such as neuropathy, retinopathy, nephropathy, or kidney disease. In the past 5 or 6 years, it has been well established that diabetic gastroparesis can also occur in Type 2 diabetes.

Potential pathogenic factors include autonomic (vagal) neuropathy, intrinsic (enteric) neuropathy, and hyperglycemia. For unknown reasons, long-standing patients develop signs of vagal nerve impairment (the vagal nerve governs motility of the proximal GI tract, especially in the stomach) and intrinsic neuropathy, affecting the enteric nervous system of the stomach. Hyperglycemia itself can impact the overall GI motility and impair stomach emptying and neural discharge. Diabetic patients in which hyperglycemia is controlled still exhibit underlying vagal or neural neuropathy.

Dr. Parkman emphasized that for patients with diabetes, gastroparesis has important consequences. Persistent symptoms lead to a markedly impaired

quality of life. Patients experience impaired oral drug absorption and poor glycemic control resulting in hypoglycemia or hyperglycemia.

Dr. Parkman summarized a study conducted by Jones et al (*Diabetes Care* 2001;24:1264) in which 101 randomly selected outpatients with diabetes (79 Type 1 and 22 Type 2) attending a diabetic clinic in an Australian academic medical center underwent a gastric emptying scan of both solids and liquids. Forty-eight percent had delayed gastric emptying; abdominal fullness and bloating and female gender were predictors of delayed gastric emptying. This was an important finding in that these patients exhibit a wide range of symptoms, although, conversely, correlation of symptoms with actual delay in gastric emptying is made much more difficult.

Analysis of prevalence of symptoms in the diabetic community has revealed that prevalence rates of symptoms are suggestive of gastroparesis (Bytzer, Talley et al. *Arch Intern Med* 2001;161:1989). Of 423 diabetic patients in a population-based Australian survey, approximately 18% had symptoms of upper GI dysmotility compared to 15% under normal circumstances. Dr. Parkman pointed out that this study, although less statistically significant, offers an important item for consideration. The prevalence of symptoms (20%) was lower than at the academic medical center, suggesting that studying patients in the community may lead to more information than focusing on those in tertiary academic medical centers. Additionally, Bytzer's study examined the relationship between gastrointestinal (GI) symptoms and overall glucose control, and discovered that the symptoms complex of upper GI dysmotility increase as control diminishes. Whether upper GI dysmotility causes poor glycemic control or vice versa is uncertain; however the relationship has been established.

Diabetes has been associated with an impaired quality of life in both physical and mental subscales. Dr. Parkman presented a study by Talley et al (Talley et al. *Am J Gastro* 2001;96:71) which demonstrated that quality of life decreased as the number of GI symptoms increased in a non-selected group of diabetic patients.

Dr. Parkman estimated that the prevalence of diabetic gastroparesis in the general population of the United States in 2000 was approximately 8%. Of those individuals, the diagnosed rate of gastroparesis in Type 1 diabetic individuals is approximately 25%, whereas in Type 2 diabetics the number is closer to 5%, resulting in nearly 1.5 million Americans with gastroparesis.

Idiopathic gastroparesis is the most common form of gastroparesis. With no underlying cause, it typically occurs in young or middle-aged women, with symptoms fluctuating between mild and severe. It has been suggested that in some individuals (20%) a precedent viral illness (indicated by acute onset of symptoms) might trigger abnormality leading to viral injury of the neural innervation of the stomach. The subsequent presence of antibodies also suggests that these patients may have had a preceding viral illness.

Dr. Parkman reported that upper GI symptoms are prevalent in the general population, with a marked increase among female versus male patients for each symptom recorded. (Camilleri, Whitehead et al. *Gastroenterology* 2000;118:A144). Early studies of patients with idiopathic dyspeptic symptoms suggest that as many as 50 to 60% of those patients with functional dyspepsia may have evidence of impaired gastric emptying. Studies in more recent years with larger subject populations suggest the number is more likely 25%. Initial studies revealed no

correlation of delayed gastric emptying and specific symptoms was identified. However, recent studies indicate that vomiting and postprandial fullness may be correlated to delayed gastric emptying in patients with underlying idiopathic dyspeptic symptoms.

The treatment of gastroparesis requires a step-wise approach involving, initially, dietary and lifestyle modification. Pharmacology, including antiemetic and prokinetic agents, is often a part of treatment. Some patients seen at tertiary centers require nutrient supplementation, and few undergo surgical resection or gastric electric stimulation.

At a recent meeting of the Gastroparesis Task Force, it was proposed that patients be divided into grades from mild (those patients with clinical or test abnormalities, compatible with gastroparesis, able to maintain weight and nutrition on a regular scale) to compensated (patients with findings of gastroparesis, able to maintain nutrition with dietary and lifestyle adjustments and pharmacologic treatments) and decompensated (an individual whose stomach does not clear simple liquids, secretions or gas and who is dependent on gastric suction/venting plus enteral/parenteral nutrition).

Dr. Parkman described a search of North Carolina nonfederal hospitals for diagnosis of gastroparesis cross-referenced to diabetes which identified 45 patients with a primary diagnosis of diabetic gastroparesis with an average hospital stay of 5 days. (Belli et al. SMJ 2002;95:1297). More interesting is that although diabetic gastroparesis was not the primary diagnosis, it was the cause of admission for another 1,400 patients with diabetic individuals who also experienced an average 5-day hospital stay, a number made even more significant by the fact that North Carolina is a relatively small state.

In terms of economic burden, Dr. Parkman summarized costs for patients with severe refractory gastroparesis from baseline data obtained prior to gastric electric stimulation treatment in which the total cost per patient per month was more than \$6,900, with an average hospital stay of 24 days per year. (Abel T et al. Am J Gastro 2001;96:S258).

Dr. Parkman described recent epidemiological steps by researchers, including the development of specific symptom-based questionnaires for gastroparesis; disease-specific quality of life instruments; standardized gastric emptying tests, such as the breath tests; and the development of a better understanding of the relationship of symptoms to delayed gastric emptying, glucose and gastric emptying, and the differences between tertiary care centers and the community.

Dr. Parkman concluded his presentation by identifying several future research endeavors:

- An investigation of the prevalence of gastroparesis in the general population;
- Determination of the natural history of the disorder, including predictors for long-term outcomes and prognosis with respect to impairment of quality of life and economic burden; and
- An improved grading system, perhaps based on gastric emptying, nutritional status, or objective tests, rather than empirical data.

### **Discussion**

In response to a question regarding qualitative versus quantitative differences between gastroparesis due to diabetes or idiopathic gastroparesis, Dr. Parkman stated that the symptoms are typically the same in both instances, except that diabetics with neuropathy often experience greater abdomi-

nal pain. With idiopathic gastroparesis, symptoms fluctuate, worsening at some times and improving even without effective treatment. Diabetic individuals are often symptomatic; despite glucose control, symptoms persist over time.

Dr. Parkman stated that idiopathic gastroparesis and functional dyspepsia are likely a continuum of physiological abnormalities. In his practice, patients presenting with gastroparetic symptoms are more likely to be diagnosed with idiopathic gastroparesis, whereas those with abdominal pain and delayed gastric emptying tend to be classified as having functional dyspepsia with delayed gastric emptying. Dr. Michael Camilleri (Department of Internal Medicine, Mayo Clinic, Rochester, MN) agreed that a continuum exists, and commented that a better understanding of symptoms, epidemiology, and mechanisms will be required before the two conditions can be differentiated. Another participant added that, from a research point of view, pigeonholing patients may do more to obscure than to clarify the pathophysiology, and that it is important to recognize the relative state of ignorance of both conditions.

Dr. Parkman explained that the study he cited in which an association between glycemic control and GI symptoms in diabetic patients was observed was based on self-reported data, not objective parameters. However, subsequent studies in a small subset of patients in which hemoglobin A1c was measured reported a similar trend as the previous study.

Validation of the grading system suggested by the Task Force has not yet been undertaken, but it was identified as a potential research opportunity. A further area of study is the identification of diabetic complications with gastroparesis which might occur in the rapidly increasing number of children and

adolescents with Type 2 diabetes. Dr. Parkman commented that some studies have suggested obesity might enhance gastric emptying, resulting in more absorption and increased weight gain; however, these reports have not been validated. Treatments have also been proposed to reverse stimulation of the stomach to treat gastroparesis.

Although longstanding obesity does not always progress to diabetes, Dr. Parkman stated that it can lead to insulin resistance which, while not diabetes by objective parameters, may nevertheless be evidence of the recently proposed metabolic syndrome and subsequent parameters of diabetes. Dr. Camilleri added that it appears obesity is associated with changes in gastric reservoir function, which is not determined solely by Body Mass Index (BMI). In fact, BMI per se probably accounts for only a small percentage of the variance in the fasting gastric volume, a point which is important in terms of drinking capacity in a standardized drinking test. However, other factors may be involved, including neurohormonal modulations that might influence the function of the stomach.

Based on Dr. Camilleri's comments, a participant suggested that it appears that there is a difference between Type 1 and Type 2 diabetes and gastroparesis. It may be that the variances between academic centers and the general population can be explained by a difference in the type of diabetes examined in the separate populations. Dr. Parkman agreed that it might be due in part to poorly controlled Type 1 diabetes in the general population versus those who are preferentially referred to in the academic medical centers.

### ***The Quality of Life Issues for Patients with Gastroparesis***

Jeanne Keith-Ferris, R.N., B.Sc.,  
President/Founder, Gastroparesis and Dysmotility  
Association, Calgary, Alberta, Canada

Ms. Keith-Ferris described gastroparesis as a debilitating condition in which the stomach fails to empty. The disorder can progress, reducing a previously functional person to an existence tied to hospitals and the emergency room. Although prokinetics and antiemetics are available treatments, they are variable in their ability to provide ability to provide relief. The disorder strikes mainly young and middle-aged women, causing frequent hospital admissions, leaving patients unable to work, attend school, or socialize.

Primary symptoms include nausea, vomiting, and abdominal discomfort from pain and bloating. Ms. Keith-Ferris brought renewed emphasis to a point made earlier in the meeting, that regardless of the means by which a patient develops gastroparesis (e.g., idiopathic, diabetes, or post-surgical), these individuals experience symptoms such as nausea and vomiting which have a major impact on their lives.

Ms. Keith-Ferris summarized data from the DIGEST study, a comprehensive international study of 6,000 patients randomly selected from the general community in 10 countries. The study looked at quality of life, cost burden, and prevalence. Vomiting had the greatest interference in daily life and was ranked most severe of the 14 digestive symptoms reported by participants (abdominal pain was second in severity, followed by nausea). Participants reporting greater symptom severity for one or more symptoms had significant impairment in quality of life scores compared with those reporting milder symptoms.

Ms. Keith-Ferris stated that experts would agree that gastroparesis is an illness whose health burden has been underestimated to date; that quality of life is greatly impacted due to the severity of symptoms (which can persist for decades) and mortality; and that death can result from interventions, complications or end-stage of a disease process.

Patients with gastroparesis face repeated hospitalizations, which not only impact quality of life, but which also represent a large economic cost burden. The 1994-1995 Annual Report of the Clinical Motility Center at the University of Tennessee-Memphis reported that motility patients accounted for 5% of total physician billings among 100 doctors at the center. Gastric Electrical Stimulation (GES) published papers document numerous hospitalizations and mean symptom duration of 6 to 10 years.

Ms. Keith-Ferris pointed out the lack of awareness among physicians which impacts gastroparesis patients' quality of life and care. Patients may be treated by physicians who know very little about the disorder, since there is little published information to guide treating physicians. Without national treatment guidelines, no consensus on the definition or diagnosis exists. Generally, physicians dislike treating these time-consuming patients for whom they have little to offer. With very few experts available in the field, accurate diagnosis may be delayed for years, and patients' upper digestive symptoms are often dismissed as stress-related. It is not unusual for patients to be considered for psychological evaluation and adolescents are frequently referred to eating disorder clinics, when in fact these individuals are gastroparetic. Total gastrectomy for intractable nausea and vomiting is not an uncommon recommendation; most patients do not elect to follow this advice, but for those who do, symptoms persist despite the surgical intervention.

Lack of awareness in the community by insurance carriers and Medicare also impact patients' quality of life and care. The legislative language in Medicare policies does not recognize gastroparesis or many other intestinal dysmotilities as debilitating conditions. Ms. Keith-Ferris stated that these patients, on average, will have to fight through two or three appeals before disability and Medicare coverage is granted. Nor do insurance companies cover the cost of all prescriptions for all patients (e.g., Ondansetron, Domperidone, etc.). Difficulty with coverage and continued coverage for medical foods (enteral and parenteral nutrition) is not exclusive to this patient group, but it does add to their burden and stress.

Ms. Keith-Ferris stated that Rentz (et al) reviewed the published literature related to gastroparesis and found that health-related quality of life is focused primarily on GERD, functional dyspepsia, and irritable bowel syndrome, with very little to report regarding gastroparesis. As mentioned previously, many of those diseases have disease-specific quality of life measures, whereas none have been identified for gastroparesis. Of those diseases listed, gastroparesis has, without question, the greatest degree of morbidity, and the patient group is undoubtedly captured in the GERD and functional dyspepsia literature, from which the impact on quality of life can be gauged.

As an indication of quality of life, SF36 scores can be an important measure. Ms. Keith-Ferris compiled data from patients in the literature and found that SF36 scores were extraordinarily low for patients treated with gastric electric stimulation even in comparison to those individuals on renal dialysis or intestinal failure from Crohn's Disease, probably due to the frequency of vomiting and nausea

reported by patients. In fact, scores for gastroparesis patients in physical functioning mental health, vitality, and across the board are significantly lower than even those with congestive heart failure. Severe gastroparesis patients must be maintained on long-term enteral/parenteral nutrition which adversely affects quality of life. Still, the treatment is not for their symptoms (debilitating nausea and vomiting persist); it simply maintains their weight.

These interventions are not without risk. Referring to the Jones literature review cited previously, Ms. Keith-Ferris said that complication rates from jejunostomy were found to be high, including infections and one reported death. Ms. Keith-Ferris emphasized that physicians and researchers ought to keep in mind that these patients must endure repeated emergency room treatment and significant complications. TPN is itself a risky procedure which greatly affects quality of life, and for those patients who are very low-weight, a full bag of TPN or enteral feeding may be close to half of their body weight.

Medical treatment does, as expected, correspond to improved quality of life measures, a finding which has been demonstrated in the published papers. However, for gastroparesis patients, those with moderate to severe gastroparesis are limited in symptomatic relief options. The two most studied drugs for efficacy in improving quality of life, Domperidone and Cisapride, are not readily available. Ms. Keith-Ferris stated that most patients must settle for treatment with standard Erythromycin, the effectiveness of which wanes over time; Metoclopramide (Reglan), which has an approximate 30% discontinuation rate because of side effects; and Tegaserod, a relatively new treatment, which has not yet been evaluated with regard to quality of life effect.

Ms. Keith-Ferris remarked that it is important to assess quality of life variables to provide a broader clinical picture of efficacy for given treatments when evaluated along with traditional symptom measure outcomes. Quality of life measures also offer vital information to tailor treatment packages to a heterogeneous patient population such as that comprised of gastroparesis patients. More importantly, measuring quality of life ensures that information gleaned is meaningful to the treatment and symptom reduction of those patients involved.

Surgical treatments are available, but are much riskier. Ms. Keith-Ferris stated that the literature review by Jones et al found that most papers focused on technique rather than outcomes and offered little information regarding correlation to patient quality of life, rendering this another area that warrants further research attention. In fact, the wisdom behind total gastrectomies ought to be more closely examined, particularly since they are often performed on young women. Some published papers report statistically significant improvement with health-related quality of life post-gastric electric stimulation, which may be applicable to the severe patient group.

Ms. Keith-Ferris identified the following areas where more information is needed and opportunities for research exist:

- Quality of life studies need to be conducted in order to help policy makers quantify, qualify, and understand the impact of gastroparesis on patients and society;
- The patients' views and priorities must be taken into account when tailoring treatments; and
- The lack of broader understanding in the medical community, the lack of treatments to improve quality of life, the degree of disability, and mortality add up to a medical crisis for these patients.

To meet these needs, Ms. Keith-Ferris recommended that a database and registry be constructed to expedite the gathering of quality of life data for researchers and policymakers.

### **Discussion**

Dr. Panka J. Pasricha (Medical Branch Internal Medicine, University of Texas, Galveston, TX) commented that the quality of life issues are striking in that they illustrate the drastic impact of this disease on patients, which is not surprising when one considers their symptoms surround the very fundamental act of eating. Very little clinical understanding of nausea exists; it ought to be given the kind of respect and attention that other symptoms receive. Dr. Pasricha recommended that an effort be undertaken to focus on nausea in a manner similar to that placed on chronic pain itself rather than its underlying cause.

The issue was raised by one participant that part of the problem with quality of life is the need for more effective treatments. Since these patients do not exhibit overt abnormalities, education is a very important approach. It may be that the message ought to be directed to endocrinologists and family practitioners to better serve these patients. Dr. Parkman agreed that informing family care physicians and internists might result in referrals to appropriate resources and better access to alternative treatments.

Dr. Pasricha remarked that another aspect of the quality of life issue involves the treatment of these patients in social and professional settings. He often receives requests from patients for letters of disability because those with acute gastroparesis suffering from constant nausea, weight loss, and vomiting are unable to perform regular work. Unfortunately, the current legal parameters for

disability do not encompass the functional disabilities experienced by these individuals. Another participant echoed these concerns, adding that the computations for disability are extremely formulated and do not include what is not visibly apparent. However, draft guidance is currently underway to address the approach to defining disabilities.

Dr. Brian E. Harvey (Associate Director, Regulatory Policy, Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD) stated that his experience at an Annapolis (Maryland) hospital on weekends emphasizes that outreach to the internal medicine and family practice communities would greatly benefit both diagnosis and treatment.

Dr. Richard McCallum (Department of Medicine, University of Kansas Medical Center, Kansas City, KS) made the observation that the depression experienced by gastroparesis patients who have suffered with chronic illness for many years without receiving satisfactory medical care is pronounced, which probably contributes to the inclination of physicians to diagnose their condition as psychologically based. Since depression is a side effect of some medications used to treat the disorder, it is important to note that the treatment itself may be a detrimental factor in psychological status for patients.

Ms. Keith-Ferris concurred with Dr. McCallum's statements, adding that the great lack of awareness in both the patient and physician communities regarding depression is often complicated by the fact that some patients who are post-viral or post-infection have gone from being very healthy to being very ill. When the medical community offers no definite diagnosis of a disorder or effective treatment of their symptoms, these patients suffer immensely devastating psychological consequences.

It may be that mere awareness in the medical community could significantly improve the quality of these patients' lives, simply through reassurance and understanding of their condition.

### ***Pathogenesis of Gastroparesis***

John Wiley, M.D., Associate Professor and Director of Internal Med-Gastroenterology Program, University of Michigan, Ann Arbor, MI

Dr. Wiley prefaced his presentation by stating that understanding of the molecular basis for diabetic gastroparesis is truly in its infancy, and that most of the following information was drawn from extrapolation of models used for the examination of diabetic neuropathy in non-enteric systems.

Most studies involving diabetic neuropathy as currently understood emanate from literature focused on primary sensory nerves (i.e., dorsal root ganglia (the repository for cell bodies that transmit sensory function from the periphery, including pain transmission and reception) and their distribution). Evidence supports region-, tissue-, and cellular-specific differences in the means by which diabetes affects function. However, some mechanisms may apply broadly. Ultimately, very little is known regarding how diabetes affects neuromuscular function at the cellular level in the GI tract.

Dr. Wiley stated that hyperglycemia is certainly associated hyperglycemia, either with decreased insulin production (the Type 1 model) and/or insulin function (the Type 2 model). A review of the literature revealed altered nerve function is associated with diabetic complications such as impaired microcirculation to the neurons and formation of advanced glycation products, diminished neurotrophin expression and/or function (leading to

clinical trials investigating the use of neurotrophin supplementation to restore impaired neural function and the examination of target-specific therapies), increased reactive oxygen species and decreased levels of antioxidants, and activation of polyol pathway and abnormal signal transduction mechanisms such as protein kinase-C. In animal models, the sorbitol pathway seems to be quite effective when specifically targeted with aldose reductase inhibitors; however, those results have not translated into effective monotherapy in human studies. Interestingly, it appears that isoforms of protein kinase-C may be relevant in diabetic complications, and as therapeutic developments allow for targeting of specific PKC isoforms, it may provide a practical application in the management of those complications.

An investigation conducted in Dr. Owyang's lab involved the use of human surgical specimens, control tissue and myenteric plexus teamed with an antibody that recognizes neural nitric oxide synthase. Results indicated that nitric oxide (NO)-producing myenteric neurons preferentially decrease in the human stomach. Dr. Owyang's lab has also measured levels of expression of NO synthase in neurons and, using Western blot analysis, has shown those levels to be decreased. Parallel studies of acetylcholine-containing neurons seem to indicate that diabetes preferentially involves a diminution in the nitric-oxide containing or-forming neurons, which may have some clinical relevance. Dr. Wiley also cited unpublished data showing that oxidative stress contributes to the degeneration of nitrergic neurons in diabetes. Similar studies have been done in the colon in diabetic animal models with comparable results.

Dr. Wiley presented potentially novel mechanisms of the pathophysiology of diabetic peripheral neu-

ropathy, including the appearance of autoantibodies in patients with evidence of neuropathy, and suggested further investigation of a possible connection between with altered calcium signaling and neuronal dropout. Future endeavors will also involve an exploration of downstream manifestations. Dr. Wiley proposed that mitochondrial dysfunction plays a role in the neuropathic process in that impaired mitochondrial function has been associated with activation of apoptosis.

Dr. Wiley introduced recently published results from a study in which serum from patients with Type 2 diabetes with neuropathy induced complement-independent, calcium-dependent apoptosis in cultured neuronal cells. The provocative aspect of this finding is the effect of diabetic serum on cytosolic calcium in SY5Y neurons (a human neuroblastoma cell line), in which an increase in the response calcium mobilization, both through influx as well as in calcium stores, was observed. Cells treated with a diabetic serum demonstrated an induction of apoptosis when compared to controls. Screening for antibodies reveals some evidence for IGM, autoantibodies involved in the IGM class and, to a lesser extent, the ITG class.

The link between calcium and apoptosis generation has also become apparent through the effect of calcium channel antagonists on diabetic serum-induced apoptosis. In fact, several articles in the literature support the use of calcium channel blockers in the management of diabetic complications. However, Dr. Wiley pointed out that the only available blockers are L-channels, the muscle channels representing a subset of the calcium channels present on neurons. In order to produce a greater response, blockage of additional calcium channels will be necessary.

Using a vital stain called JC1 (which loads the mitochondria and then, depending on the membrane voltage of the mitochondria, changes from a monomer to an aggregate, reflected in an alteration in fluorescence pattern), a ratio representing the degree of mitochondrial depolarization can be observed. Under basal conditions, the diabetic DRGs were more depolarized than controls; in culture, the diabetic cells depolarize to an even greater extent than do the control cells.

Dr. Wiley described an animal study in which an insulin intervention was introduced to diabetic rats between 1 and 2 months following induction of diabetes. Within 2 weeks of treatment, using insulin to normalize blood sugar, it was possible to reverse the mitochondrial abnormalities, also translating into reversal of the apoptosis. The animal model showed a decrease in the anti-apoptotic mitochondrial localized product, Bcl-2, cytochrome c was translocated from the mitochondria to the cytoplasm, and caspase 3 and TUNEL were activated. The presence of apoptosis using both caspase 3 as a marker as well as TUNEL has been also been indicated in a study which showed that neurons that are double-labeled with a marker for neurons demonstrate an elevation in activation of caspase 3, accompanied by a parallel activation of TUNEL. Insulin treatment introduced for 2 weeks between 1 and 2 months following the onset of diabetes again reversed the induction of the apoptosis.

Prior to introducing an unpublished concept that may have potential importance as a contributing factor to neuropathy as applied to diabetes, Dr. Wiley provided definitions of the three subtypes of programmed cell death (PCD): Type 1, apoptosis (caspase-dependent, nuclear fragmentation); Type 2, autophagic (caspase-independent, vesicular

sequestration of injured organelles); and Type 3, non-lysosomal vesiculate degeneration. The current focus is on Type 2 PCD and the expanding role of autophagy in pattern development, cellular response to stressful conditions, cytoprotection, its presence in neurological disorders such as Huntington's and amyotrophic sclerosis, and its potential role in the aging process.

Transient nutrient removal and hypoxia are commonly employed techniques to induce autophagy in a variety of cells. To determine whether the same pathway could be stimulated in the neurons of diabetic cells and to identify the circumstances under which stimulation occurs, investigators used a dorsal root ganglia model and a two classic markers—a microtubular-associated protein-1 (LC3) marker specifically localized to autophagosome membranes, and beclin-1, which localizes in the transvillagic network and links to Class III phosphatidylinositol 3-kinase complex, a signal transduction pathway thought to play a critical role in the activation of autophagy. Study results indicated a robust activation of the pathway in a number of diabetic rat cells when compared to the controls. Similar studies are currently being planned using an enteric nervous system model.

Continuing to examine the autoimmune concept, serum from Type 2 diabetic patients with documented neuropathy was compared to human serum from patients without neuropathy in an effort to determine whether or not the pathway was activated. Again using classic markers and neuroblastoma cells, the induction of the pathway was demonstrated.

Dr. Wiley presented a standard Western blot illustrating that SY5Y cells treated with serum results in a very strong activation of the PI3-kinase Class III

pathway, representing a potentially highly specific pathway target. Antagonism of diabetic serum-induced autophagy by PI3-kinase inhibitors has also been observed, providing further support for a potential target.

Additional evidence of an autoimmune element was demonstrated through the use of immunoglobulin-binding agarose beads. Exposure of Type 2 diabetic serum to protein L agarose beads reversed induction of autophagy.

Signal transduction has been studied using diabetic serum screened for Fas (CD95), a so-called death domain receptor pathway. A very similar activation was observed in diabetic serum-exposed cells compared to a tumor necrosis factor seen in the control cells. Further evidence has been provided by the observation of a vigorous increase in the analysis of protein levels of the Fas-activated death domain pathway present in normal diabetic serum.

In summary, Dr. Wiley stated that autophagy and apoptosis may contribute to the pathophysiology of diabetic complications, and that autoimmune mechanisms may contribute to the natural history of both autophagy and apoptosis, the latter of which has been linked to autoimmune mechanisms in the case of Type 1 diabetes on Islet cells.

Dr. Wiley identified several unresolved issues requiring further elucidation including: Is autophagy an initial cytoprotective response to cellular stress? Alternatively, is autophagy a parallel pathway to apoptosis and programmed cell death? It may also be that the two are linked in some manner; although the few most recent reviews suggest that the two pathways are parallel and independent, preliminary data may provide evidence that there are points of interaction between them. Dr. Wiley stated that clar-

ifying the cellular mechanisms associated with diabetic complications affecting the GI tract will likely lead to novel therapeutic interventions. The multifactorial nature of the mechanism(s) underlying the pathophysiology of diabetic complications will probably require combination therapies rather than monotherapy in order to achieve a durable and beneficial level of efficacy suitable for the patient population.

### ***Discussion***

A comment was made that the literature about neuropathies in diabetes, as well as in other similar GI disorders, points out the apparent inability of histologists to make a simple assessment of loss of neurons. In response to a question regarding the availability of neuron counts in long-term diabetic patients with evidence of gastroparesis, Dr. Wiley stated that there is a need for research in the area of neural subtype populations. Existing literature suggests there may be a gradient in the digestive tract in terms of the effect of diabetes; however, literature on the dropout of total numbers of neurons in diabetics is only now being clarified. Some of the evolving literature concerning neuronal subtypes that may be preferentially at-risk depending on the nature of their transmitter milieu may ultimately offer needed insight, as well as examination of nitric oxide synthase-containing neurons.

Dr. Wiley stated that the natural history of diabetes is slowly progressive. Part of the controversy surrounding neuronal dropout in death and the magnitude of that phenomenon centered on the use of extremely hyperglycemic in vitro conditions which produced very high levels of apoptosis, inconsistent with the natural history of the disease in which clinical manifestations often do not become apparent until a decade or more of progression. Dr. Owyang

added that recent morphometric studies indicate the dropout is a questionable and selective problem.

One participant expressed interest in these remarks, since in most cases, NOS is expressed with IP, suggesting a selective decrease in NOS expression rather than NOS neurons. Inhibitory fibers may be present even if they no longer express nitrous oxide, a sort of phenotypic expression. It was recommended that a radiometric expression analysis be undertaken to demonstrate the change in phenotypic expression.

Dr. Wiley directed a response to a question regarding long-term effects, stating that the regenerative capacity of an adult enteric nervous system is relatively limited. Recent brain and spinal cord studies may provide data to suggest the existence of a very small subpopulation of cells with regenerative capacities that could be induced. Dr. Owyang commented that the regenerative process is probably slower than many other neural injuries, possibly due to the external damage which occurs in diabetic neuropathy.

Dr. Pasricha raised the issue of questioning the importance of neural regeneration versus phenotypic expression, since very specific neurotransmitters and long-term devastation is involved. He pointed out that subsets of patients need to be recognized both within and outside of diabetic gastroparesis, which has a variable natural history, and recommended further research in the areas of idiopathic gastroparesis and the possibility that the serum factor in downstream signaling patterns may or may not be TNF. Dr. Wiley stated that the histopathology does not typically indicate the occur-

rence of much cellular-mediated neural injury. The microcirculation literature is evolving, and part of the issue being investigated is that capillary supplies to neurons may well be impaired as part of the complicating feature of the neurons.

### ***Remodeling of the Rhythmo-neuromuscular Apparatus in Diabetes***

Kenton Sanders, Ph.D., Department of Physiology and Cell Biology, University of Nevada School of Medicine, Reno, NV

Dr. Sanders offered a brief physiological explanation of the stomach and its functions as a complicated organ. Following ingestion, the proximal stomach first expands in size and then slowly contracts, moving stored material into the distal pump for further processing. From the scintigraphy in earlier talks, it would appear that the main disorder occurs from food remaining in the fundus. When solid material is consumed, the antrum has to produce peristaltic contractions that slowly grind up the material until it is emptied through the pyloric sphincter. Finally, when food moves into the duodenum, it must be cleared. Problems with any of the different motor functions could produce changes in gastric emptying; investigators may be looking at a syndrome resulting from a multitude of possible factors. [A video presentation depicting fundic compliance was shown to participants.]

It has been fairly well reported that a group of cells called Interstitial Cells of Cajal produce the phasic electrical activity responsible for gastric peristalsis, which occurs continuously, independent of episodes

of fasting or feeding. Dr. Sanders emphasized that that this slow-wave activity is conducted through the smooth muscle cells not in them. The response of the smooth muscle cells to depolarization of slow waves is to activate L-type calcium channels. Contractions are timed by these electric slow wave events, and the response of the musculature is also tuned by input from the enteric nervous system and the presence of both excitatory and inhibitory inputs. The release of excitatory transmitters tends to increase the ability of the slow wave to produce a contractile response, whereas the release of inhibitory transmitters causes a reduction in that ability.

Dr. Sanders pointed out that the enteric nervous system does not appear to communicate very well with the smooth muscle directly. It seems another type of interstitial cell acts as a translator so that release of the neurotransmitter is mediated through intramuscular interstitial cells. Much of recent work in this area has focused on Interstitial Cells of Cajal because of their very important role in generating slow-wave activity and mediating responses to neural input.

Diabetic gastroparesis in the literature dates to the 1940s, when it was noted that similarities in symptoms experienced in patients with vagotomy suggested that disordered gastromobility in long-term diabetes may be due to vagal damage.

Cardiovascular autonomic function is usually used to assess the degree of diabetic neuropathy because it is difficult to clinically assess GI autonomic functions directly. Dr. Sanders stated that the incidence of patients with gastroparesis and disordered gastric motility is clearly higher in patients with cardiovascular autonomic neuropathy. However, the correla-

tion between disordered gastric motility and cardiovascular autonomic function (either by sympathetic or parasympathetic parameters) is relatively weak.

There has been some recent and very good progress using animal models to evaluate neuropathies and diabetic gastroparesis. Morphological changes have been reported in autonomic nerves supplying the gut, reduction in myelinated axons in the vagosympathetic trunk, and neurons in the dorsal root ganglion. Deficiencies have been noted in neurotransmitters, such as serotonin, calcitonin, CGRP, Substance P, neuropeptide, and keffin, but no functional evidence has yet been linked to these changes in disordered gastric motility, and very little evidence exists to link any of these observations to human diabetes.

Dr. Sanders stated that reduced expression of nitric oxide synthase by enteric neurons with NOS immunoreactivity and nacreal relaxation has been demonstrated in animal models and in humans, a finding which could be very important when considering the mechanistic responses for defective gastric accommodation in diabetic gastroparesis.

In NOD and streptocytosin-induced diabetic mice, defects in gastric emptying and relaxation of the pyloric sphincter have also been shown which resemble defects in knockout mice, possibly indicating a link between functional and reduction of NOS in those animals. These defects can be reversed by insulin and with type 5 phosphodiesterase inhibitor Zenofidil.

Trunkal vagotomy and blockage of nicotinic receptors reduced non-allergic, non-cholinergic relaxation of gastric muscles, the catalytic activity of NOS, the number of NOS immunoreactive cells, and the den-

sity of NOS immunoreactive bands in NOS MRNDA bands obtained from gastric tissues.

Dr. Sanders described gastric-emptying studies conducted on a NOD (Type 1 diabetes animal model), showing normal gastric-emptying patterns for solid meals in mice and greatly compromised rates of gastric emptying in long-term diabetic mice 2 months after diabetes was diagnosed. Those findings were corroborated with liquid meals by Johns Hopkins investigators, who compared the solid meal results to streptocytosin diabetic and nNOS knockout mice. The pyloric sphincter was contracted, followed by stimulation of inhibitory nerves and subsequent relaxation. In the NOD diabetic animals (as in the NOS knockout mice), comprised relaxation and relaxation response was noted, which could be largely improved by insulin treatment. The streptocytosin animal treated with insulin also demonstrated recovery, indicating that this model is appropriate for pyloric sphincter defect knockout. As shown by Dr. Owyang's group, there was a reduction in NOS expression in the NOD mouse, which could be partially recovered by insulin.

Neural defects in electrophysiology have also been observed in the rat gastric antrum. Dr. Sanders summarized data from a study in which a reduction in neural response to stimulation was demonstrated. The typical response of muscles from the antrum is a small depolarization mediated by acetylcholine, and a large hyperpolarization largely mediated by nitric oxide. Consistent with the idea that NOS expression might be decreasing, a much smaller amplitude inhibitory effect was observed. However, cholinergic effect was also lost, indicating that not only does a loss of nitric oxide occur, but that other enteric neurotransmission may also be affected. Data from this study also showed the effect of streptocytosin on antral hypomotility which was associated with changes in slow wave activity.

Dr. Sanders stated that although slow wave activity is closely connected to other types of cells, the action is completely separate from nerve cells, requiring researchers to investigate other explanations for patients' symptoms. Neither can the involvement of Interstitial Cells of Cajal provide a complete explanation for the findings present in the diabetic stomach.

*[In an aside, Dr. Sanders clarified the two classes of interstitial cells in the stomach: an intermuscular type that mediates neuromuscular transmission and one that produces pacemaker activity. These cells line the entire phasic region of the stomach, from corpus to pylorus.]*

As previously stated, an event begins in the greater curvature of the stomach that produces a generalized excitation that spreads around the stomach very rapidly and then spreads as a band down to the pylorus. At any point, records from the stomach indicate the presence of the electric slow wave, a sort of carrier wave taking the peristaltic event from the corpus region to the pylorus. This activity is critical for distal antral motility.

Using kit immunoreactivity that labels interstitial cells, researchers found a profound decrease in the numbers of interstitial cells present in diabetic tissues of NOD mice which have been diabetic for approximately 2 months. The loss of cells was not complete, in that patchy lesions were observed, together with some areas that had no interstitial cells and others with compromised networks. Little effect was seen in the corpus region; however, when cells from the region were impaled in the antrum, quiescence was observed, indicating some areas were not being invaded by slow wave activity and therefore could not respond during gastric peristalsis, contributing to antral hypomotility. Researchers also found generalized reduction in response to

nerve stimulation because of either loss of intramuscular-type interstitial cells or a weakening in the tight relationship between those cells and the enteric neurons.

Dr. Sanders described a human study at the Mayo Clinic which focused on loss of interstitial cells in insulin-dependent diabetics and a decrease in inhibitory intervention, and a Japanese study of the deficiency of kit positive cells in the colons of patients with diabetes mellitus. Dr. McCallum's group has shown that an absence of Interstitial Cells of Cajal in patients with gastroparesis has a correlation with clinical findings. Results such as these suggest some similarities exist between the mouse and human models in terms of interstitial cell expression.

Gastric dysrhythmias have also been associated with some gastroparesis patients. Several clinical conditions are related to disturbances in gastric slow frequency and may also be related to induction of nausea and vomiting due to gastric stasis or antral hypomotility. Studies of humans and animals have indicated multiple neurohumoral factors may be involved in the generation of gastric dysrhythmias. For instance, antral distention and increased intestinal delivery of lipids may cause slow wave disruption and development of nausea. This may be medicated by cholinergic or serotonergic neural pathways.

Progesterone and estrogen levels have been linked to disruption of gastric slow wave rhythms in susceptible individuals, a particularly interesting finding given the high incidence rates in females. Prostaglandin overproduction in gastric muscles appears to mediate slow wave disruption in diabetes and in response to nicotine. Central cholinergic pathways seem to be involved in gastric dysrhythmias associated with motion sickness, and these

may be mediated by vasopressin released from the pituitary. Dr. Sanders listed new therapies which may either help to eradicate dysrhythmias or reduce the symptoms, including central muscolinic receptor inhibitors, prostaglandin synthesis inhibitors, dopamine receptor antagonists, and electrical stimulation.

The importance of electric dysrhythmias in the stomach lies in the frequency gradient that occurs in that organ. In the orad corpus near the pacemaker region in the human, slow waves run off at about three per minute. However, moving away from that point, sample tissues reveal slow waves running at only one per minute. Dr. Sanders explained that the intrinsic pacemaker of antral frequency is only a fraction of the dominant corpus pacemaker. Thus, there is time in the stomach for the event to propagate from the fundus to the antrum, and therefore the corpus drives antral motility, resulting in an orderly progression of peristaltic contractions in the stomach. Unfortunately, in some cases, ectopic pacemakers can occur, causing dysmotility to be generated in which the antral pacemaker runs at too high a frequency, with subsequent disorderly propagation and disruption. Without time to propagate to the antrum and entrain activity, the antrum becomes functionally uncoupled from the dominant pacemaker, the normal proximal distal activation fails, and reduced peristalsis occurs.

Dr. Sanders emphasized the point that current clinical assays make it difficult to determine this type of lesion. If the frequency of antral pacemakers is only two and a half or three times per minute, an assay from the external surface with electrogastrogram may not pick it up. Although difficult to evaluate this type of defect in a patient, it would produce dysfunctional uncoupling between regions, compromising the gastric peristaltic signal and delaying gastric emptying of solids.

Investigations of the causes of dysmotility and dysrhythmias in the stomach include studying the effect of prostaglandins in producing arrhythmias in antral ICCs due to EP3 receptors, suggesting EP3 receptor antagonists could well become a very useful drug for treating dysmotilities related to prostaglandin overproduction. The M3 isoform of muscarinic receptors is also involved with the dysmotility effect; atropine is sometimes helpful. Currently, researchers are utilizing a model of cell frequency regulation, hoping to produce results which will lead to new types of therapy.

Dr. Sanders described a WWV mouse model with spotty lesion of the pacemaker-type interstitial cells and a total loss of intramuscular cells throughout the stomach, which may be a valuable model for non-diabetic gastroparesis, since idiopathic gastroparesis has been linked to the loss of interstitial cells. A technique has been used to remove interstitial cells from normal mouse tissues (and may soon be applicable to human tissues, as well), to determine the effect of loss of interstitial cells from tissues. The method has been used in mouse organ cultures with a neutralizing antibody-2 kit, resulting in a reduction in the number of interstitial cells. Given to animals, the neutralizing antibodies produce motor pathologies in the whole animal.

Dr. Sanders stated that unpublished data from Dr. Thomas Ordong's recent work suggests that hyperglycemia does not appear to be the cause of this change in interstitial cells. Instead, Dr. Ordong found that high glucose, at least in the culture, tended to aid the tissues. When insulin was included in the cultures, normal function and ICC populations were nearly restored. In addition, the insulin like growth factor, IGF1, also had some curative or restorative effects on ICC loss.

The WWV model shows a dramatic loss of ICCs across the tissue in the corpus, and a spotty lesion area that does not receive slow wave stimulation. This finding is interesting in that a similarly dramatic drop in interstitial cells occurs in idiopathic gastroparesis cases. Dr. Sanders recommended future research endeavors ought to include a determination of the association between these findings and loss of function. Dr. Ordong found that, unlike normal animals with vast slow waves in the corpus and slow waves in the antrum, WWV animals recorded from the corpus and the antrum showed slow waves present in the antrum occurring at the same frequency as in the corpus.

In summary, Dr. Sanders stated that focal or diffuse depletions of pacemaker ICC networks cause loss of electrical slow waves in the affected regions. The most likely consequence of reduced pacing of the smooth muscle musculature is hypomotility of affected areas. ICC depletions also impair slow wave propagation, so that even with normal slow wave activity in one region of the stomach, it cannot propagate to the areas where ICCs are no longer present.

Impaired slow wave propagation may display a directional heterogeneity, depending upon the patterns of ICC loss. For example, there may be preferential loss of circumferential connections in the ICC MY network that leads to impaired circumferential propagation of slow waves.

Depletion of IC in vivo leads to remodeling of the intrinsic frequency of antral pacemaker cells, increasing the pacemaker frequency up to the level of the corpus ICC. Thus, along with the loss of these cells, remaining cells display antral tachyarrhythmia which is only to the frequency of the corpus. While not dramatic, this increase in antral frequency

causes breakdown in the corpus-to-antrum frequency gradient which is fundamental and produces functional uncoupling of the mechanism responsible for gastric peristalsis, which may explain the delayed gastric emptying seen in WWV animals.

### **Discussion**

Dr. Camilleri stated that although clinicians can document that their patients have vagal neuropathy and dropout of interstitial cells or other intrinsic nerves, what is surprising is that patients' symptoms are not continuous. If neuropathy alone were responsible, the problem would have to be persistent. Since that is not the case, there may be other cofactors involved. One of the greatest challenges is for clinicians to provide treatment which allows longer symptom-free cycles for their patients.

Dr. Sanders agreed with Dr. Camilleri's statement, and added that patient susceptibility is an important issue to consider. Currently, investigators are looking at very small time windows (e.g., when dysrhythmia is observed) in animal models. By simulating those changes in tissues, they hope to determine when the first changes occur. Large-scale comparisons between genetic changes in diabetic and non-diabetic gastroparesis mouse models may reveal signatures between the two. If similar gene set changes are found in human biopsy material, it would aid not only in validating the model, but in giving new targets for treatment.

Dr. Sanders also pointed out that tissue from gastrectomies can provide valuable information and should be retained for genetic, immunohistochemical, and possibly functional analysis.

Dr. Pasricha commented that a more immediate concern than gastric emptying per se is how to treat

patients' nausea. He emphasized that, in terms of pathophysiology, a focus needs to be placed on the primary debilitating symptoms of nausea and vomiting. A participant suggested that since antral distention has been shown to induce nausea as a reflex, it may be an important aspect to consider, either from the perspective of antral hypomotility or from improper compliance issues in the upper stomach. Discussion followed regarding whether clinicians ought to concentrate on sensory observations or patient perception.

### **Medical Treatments for Gastroparesis**

Michael Camilleri, M.D., Department of Internal Medicine, Mayo Clinic, Rochester, MN

Dr. Camilleri stated that, before treatment can be prescribed, a definite diagnosis of gastroparesis must be reached. Clinicians should first exclude rumination syndrome and perform a gastric emptying test. Pressure and electrical profiles are optional diagnostic procedures. A patients' limited repertoire of symptoms (i.e., fullness, bloating, and nausea) may reflect dumping or dysaccommodation which would not respond to a prokinetic. Obstruction can be excluded using endoscopy and radiological imaging, and iatrogenic disease should also be excluded.

Medications such as tricyclics, calcium channel blockers, and even some antibiotics used to treat iatrogenic disease can cause severe contractions of the stomach, inducing many of the same symptoms seen in gastroparetic patients. Newer approaches to treatment for postprandial hyperglycemia in diabetics (e.g., GLP-1 and amylin or pramlintide) have effects on stomach emptying (Vella, Lee, Camilleri, Rizza et al. *Neurogastroenterology and Motility*, 2002).

Prior surgeries, including laparoscopic fundoplication, gastric/esophageal surgery, and variceal injection are associated with upper GI symptoms that are virtually identical to those of dyspepsia or gastroparesis.

Dr. Camilleri pointed out that symptoms arising at the start may not solely reflect impaired gastric emptying. He referred to earlier comments regarding the recognition of nausea as an important symptom and the possibility that symptoms arise either because the stomach is being distended in the antral portion by food or from an abnormal relaxation response, ought to be considered.

In the past, physicians placed a balloon in the stomach, added pressure within the balloon using a barostat, gave a meal, and recorded the increased volume response of the stomach. Several groups are now developing less invasive techniques for the measurement of this reflex response. Dr. Camilleri's group is using SPECT imaging after intravenous protectantates. Other groups have effectively used ultrasound or MR imaging. There may be other dimensions of stomach or upper GI function that will need to be investigated as part of a continued attempt to understand the genesis of symptoms in patients with these upper GI syndromes.

Results from a recently completed study of 214 patients revealed that 25% of patients with functional dyspepsia actually had delayed gastric emptying, so that they could be considered to also have idiopathic gastroparesis. However, a number of those patients with functional dyspepsia and approximately 35% of patients with diabetes mellitus and upper GI symptoms suggestive of dyspepsia exhibited impairment of the volume response of the stomach following a meal, indicating an abnormal accommodation response. It may be that restoration of nitrog-

ic function in the stomach is an alternative method to resolve these patients' symptoms, a hypothesis that warrants further research and formal testing.

Physicians presented with a patient ask themselves a series of fundamental questions, including whether the patient's symptoms are chronic or acute and whether the disease is due to a neuropathy or a myopathy (in diabetics, the disease is usually due to an either an extrinsic or an intrinsic neuropathy or a combination of both). In addition, physicians assess the patient's state of hydration or nutrition, and determine whether or not other regions of the gut are affected.

Dr. Camilleri summarized current principles of management:

- Support hydration and nutrition;
- Stimulate prokinetics;
- Provide symptom relief, preferably without the use of narcotics, which can aggravate the management of motility disturbance, and cautious use of antiemetics such as Compazine or Trifluoperazine; and
- Endoscopy and surgery.

Intravenous Erythromycin is a very effective drug for moving a patient with gastroparesis beyond an acute crisis, with use of Metoclopramide as a second-line drug. A patient with subacute or chronic gastroparesis and impaired gastric emptying is more commonly treated with p.o. Metoclopramide, 10 milligrams TID, or off-label use of Tegaserod, 6 milligrams TID. Octreotide is used if the patient presents with bacterial growth in the intestine.

Dr. Camilleri described data illustrating the effects of Tegaserod in accelerating gastric emptying in small bowel transit in healthy individuals. Variation was noted in the gastric emptying, such that placebo

seemed to produce a substantial improvement in gastric emptying. However, Tegaserod administered at 6 milligrams TID and QID appeared to be better than placebo in those studies.

Symptom responses have not been reported, and, together with quality of life, need to be formally assessed with prokinetic agents.

A recent study of the effects of Octreotide in healthy people showed that its administration resulted in delayed solid gastric emptying. The drug is used to induce a migrating motor complex in the intestine, usually within 5 minutes of injection. However, Dr. Camilleri stated that Octreotide delays gastric emptying when given with food. Therefore, it is typically prescribed (25 to 50 micrograms sq) at least 2 hours after the last meal, at bedtime, with the goal of inducing a migrating motor complex to move bacteria and residue out of the gut and small intestine into the colon (von der Ohe, Camilleri et al. *Gut* 1995;36:743-8).

Two approaches of experimental pharmacotherapy are examining the use of motilide and phosphodiesterase 5 inhibitors. An uncontrolled trial of injection of botulinum toxin into the pylorus of diabetic mice with gastroparesis produced promising results, and phosphodiesterase 5 inhibition reversed delayed gastric emptying in rats, but controlled trials still need to be conducted (Watkins, Snyder, Ferris. *JCL* 106(2000);373-384).

Dr. Camilleri remarked that often pylorospasm is associated with impairment of antral function, and that increasing cyclic GNP and replacing nitroergic innervation may actually reduce antral motor function further. It is unclear whether clinical trials using Zenofidil in either healthy or diabetic subjects in relation to gastric emptying would show relax-

ation of the pylorus to help emptying of liquids to be an advantageous outcome; however, any deleterious effect on antral motor function is clearly an important consideration.

Another interesting point is that, if motor dysfunction is restricted to the pylorus, it may be possible to inject botulinum toxin into the pylorus to aid in gastric emptying. Certainly, promising results were initially reported by Brian Lacey and the larger Temple series, but controlled trials are needed for both.

Dr. Camilleri stated that it is important to understand not only the mechanisms involved, but also the pharmacology of the drugs being used. He described ABT229, which had a superb pharmacological profile in vitro, but which, like many motilides, rapidly downregulated. In fact, in one study, placebo performed better for some symptoms than the ABT229. In both in vitro and in vivo studies, it has been demonstrated that the prokinetic effect of this medication is very rapidly lost (within 24 to 48 hours). Another problem with the ABT229 trial was that researchers did not address gastric emptying at the end of the 8-week study, so no conclusions can be drawn with respect to prokinetic action and symptom relief.

Dr. Camilleri offered brief comments on several studies of drugs which showed some acid resistant macrolides had minimal antibody activity and direct action on muscles, whereas some motilin receptor agonists demonstrated a greater affinity than Erythromycin. (Other motilin agonists such as ABT229 showed tolerance.)

With regard to botulinum toxin, the rationale may be that pylorospasm occurs in patients with gastroparesis, but it is important to remember that just

proximal to the area where that occurs, the antrum is not contracting. Data from Temple shows a trend toward improvement in gastric emptying of solids and the improvement of symptoms. Unfortunately, studies in this area of investigation have all been uncontrolled trials to date. James, Ryan, and Parkman (Am J Physiol 285:G291-G297, 2003) provided data which explained the basis for Temple's results. Dr. Camilleri shared an illustration of the contractile response to electrical field stimulation in response to different doses of Botox relative to atropine, which resulted in a reduction in contractions in response to electrical field stimulation both in the antrum and the pylorus. These results indicate caution needs to be taken if the same procedure is conducted in clinical practice, because if the injection moves away from the pylorus into the antrum, antral contractivity may actually be deleteriously affected.

Surgery is used primarily for access for nutrition and decompression. The efficacy of pacing is unclear and further studies in this area are needed. Completion gastrectomies for patients following post-surgical gastroparesis are only very rarely necessary.

Dr. Camilleri concluded with the statement that gastroparesis continues to be a clinically challenging disorder to manage. Therapy remains suboptimal, with only a weak evidence basis for many of the currently used therapies, and challenges in classification persist in part because of the relatively small number of patients evaluated from which it is difficult to draw informed conclusions.

### **Discussion**

Dr. Owyang asked Dr. Camilleri to comment about reports suggesting that combining prokinetic agents with tricyclic compounds may be helpful in some patients with gastroparetic symptoms. Dr. Camilleri stated that it may be a question of hypersensitivity in those patients, and that tricyclic antidepressants may be beneficial for the control of some patients' symptoms. He added that it may be possible that tricyclics are having a central or peripheral effect, and again emphasized the point made earlier that the most effective approach may involve more than a single therapy.

In response to a remark regarding Botox treatment of the pylorus and the important role of the pylorus in maintaining a barrier against bile reflux into the stomach, Dr. Camilleri agreed that research in the area of quantitating duodenogastric bile reflux needs to be expanded, especially since patients with impaired gastric emptying experience gastroesophageal reflux, a risk factor for development of Barrett's metaplasia.

Dr. McCallum asked if it has been observed that, given the prokinetic and antiemetic properties of drugs being used, physicians are either knowingly or unknowingly converting tachygastria back to a normal rhythm or whether the hope is that blocking nausea and stimulating motility will result in normal muscle action. Dr. Camilleri responded that significant conclusions cannot yet be drawn from studies on uncoupling of the ventricle rhythm. Once measurements can be made from two separate sites at the same time, a correlation analysis can be conducted, and improved technology will provide algorithms to evaluate the intragastric conduction of the electrical wave rhythm within the stomach.

### ***Gastric Pacing: Is This a Viable Option for All Patients?***

Richard McCallum, M.D., Department of Medicine, University of Kansas Medical Center, Kansas City, KS

Dr. McCallum thanked Dr. Hamilton for his long support and loyalty to the American Motility Society over the years.

Traditional therapy for gastroparesis has struggled for some time. Nutritional support and antiemetic/prokinetic therapies are used, and often physicians have very good results with jejunostomy tubes. Total gastrectomy is a last resort, especially since simply freeing the stomach may not relieve nausea caused by small bowel dysmotility and dysrhythmia.

More recently, researchers have become interested in the concept of “gastric pacing,” an application of an electrical stimulus that activates contraction of gastric smooth muscle, entraining at the rate of the intrinsic slow wave by a low frequency, high energy method. This method is opposed to neurostimulation, the activation of nausea and vomiting control mechanisms utilizing a high frequency, low energy stimulation to achieve symptomatic relief. Both temporary external or implantable devices are used.

Dr. McCallum described the methodology for gastric pacing, and stated that the four pairs of pacing wires are placed on the serosa of the stomach along the great curvature, at intervals of 2 to 3 cm. The most distal electrodes are placed 2 cm above the pylorus. Gastric pacing has been shown to improve emptying and symptoms in patients with gastroparesis (McCallum et al., *Gastroenterology* 1998;114:456-461).

Dr. McCallum presented a depiction of The Enterra System, which utilizes an implantable neurostimula-

tor and two neuromuscular leads. Stimulation parameters include amplitude, pulse width, rate, and cycle on/off times. As of February 2004, 135 patients have been implanted with this device at the Kansas University Medical Center, 80% of which are women. Mean age is 37 years, 93% are Caucasian. Of those individuals receiving implants, 65% are diabetic, 17% have been diagnosed with idiopathic gastroparesis, and 13% with post-surgical gastroparesis. Normal gastric emptying was 5%. Significant improvement has been observed in nausea, vomiting, upper GI symptoms, and quality of life in these patients. At 12 months, BMI had significantly improved, with removal of 90% of jejunostomy tubes and no necessity for TPN. Additionally, there was reduction in HbA1c in diabetics at 12 months. No significant acceleration in gastric emptying was demonstrated (20% of diabetics have normalized at 1 year; “viral” idiopathics can resolve over time). Hospitalization days were reduced, and continued evidence of safety and low complication rates (6% infections) have been documented. In fact, 25 to 30% of patients with the device have exhibited limited (less than 25%) clinical response.

Dr. McCallum offered a number of theories for Enterra’s success. It may be that activation of central mechanism for nausea and vomiting control is related to the constant high-frequency stimulation of the stomach wall. Augmentation of the amplitude of the gastric slow wave after eating may also be an influence. Another theory states that enhanced relaxation of the proximal stomach results in better accommodation. And finally, a small improvement in gastric emptying (20% of patients have normalized emptying), may be the explanation.

Dr. McCallum described a study in which multipoint stimulation of three electrodes (integrated by a program) in the stomachs of dogs demonstrated that multipoint stimulation is the most dramatic method

for improving gastric emptying of liquids when compared to single stimulation and placebo.

Cells of Cajal are, as previously discussed, noted to play a role in humans. Dr. McCallum's group has shown that approximately one-third of their patients (mainly those who were diabetic) actually had depleted or absent Cells of Cajal populations. Those individuals experienced more tachygastric, more symptoms, and did not respond as well to the low-energy, high-frequency gastric stimulator. This is a marker that will probably not be overcome by the current methodology.

Dr. McCallum listed several future research opportunities in this area, including:

- Identifying mechanisms of how the Enterra device has successfully reduced nausea and vomiting;
- Developing a "gastric pacing" device that will combine nausea/vomiting relief with improved gastric motility, normalizing dysrhythmias and accelerating gastric emptying;
- Exploring Interstitial Cells of Cajal (ICC) in humans to understand correlations with symptoms, diagnostic tests (EGG) and treatment outcome;
- Exploring endoscopic placement of electrodes; and
- Expanding the concept of "pacing" for the small bowel, colon, and obesity.

### **Discussion**

In response to a question from the audience, Dr. McCallum stated that the Enterra System is not placed laparoscopically, since concerns were raised with the device's positioning and longevity using that type of procedure. Only two surgeries to correct lead displacements have been necessary, for instances when the patients fell and the leads were abruptly removed from the stomach.

Displacement is diagnosed by x-ray and by interrogating the device.

Dr. Pasricha asked whether there was a divergence between the diabetics and idiopathic gastroparesis patients in the 135 individuals treated at the medical center. Dr. McCallum answered that the major red flags seen in the 30% of patients in which the device did not work or did not perform well included narcotic problems (both pre- and post-device insertion), provocative events, migraine headaches, possible cyclic changes in diabetic control, infections, and missed diagnoses for latent eating disorders. He added that idiopathic individuals are not predictable.

The fundamental issue of rationale for this form of treatment was raised. Since the electrodes are placed 10 cm away from the pylorus and individuals are administered high-frequency stimuli approximately two-thirds of the way down, Dr. Pasricha asked whether a ripple effect has been observed, either proximally or distally. Dr. McCallum stated that nothing has been distally, and that serosally, at 300 microseconds, the stimulation has no effect on the slow wave. However, a participant asked whether clustering the pulses might result in hitting excitatory neurons that are activating slow waves. Because of the slight increase in amplitude, it appears that the device is dominantly hitting excitatory neurons.

A participant stated that sequential pacing studies were published as early as 1998, and asked Dr. McCallum to explain the reasoning behind continued adherence to a paradigm which does not seem to work very well. Dr. McCallum stated that the company believes the effort expended to bring the device to this point has been worthwhile, especially given the stringent requirements of FDA device approval.

A participant commented that the effect of the device remains long after it has been turned off, which suggests the occurrence some conditioning effect, and may argue for using less invasive, external devices. Dr. McCallum responded that studies are currently being conducted to investigate the relevance of a central pathway.

Dr. McCallum was asked to clarify the choice of the signal intensity which was determined in preliminary studies. Initially, the device was slowly turned up from 1 or 2 milliamps to 5, 300 milliseconds, until a point was reached where pacing was not used. It may be that the group could have been more investigative, but the pacing parameter was established and they moved forward with it.

Dr. Pasricha offered a response to an earlier question regarding electrical field stimulation. His group has done a study in dogs where stimulation was given to the entire stomach by strategic placement of the electrodes, resulting in field stimulation rather than point stimulation. Within half an hour, a significant effect from gastric emptying was observed, suggesting that there is more to the process than simply capturing a particular neuron and evoking neurotransmitter release.

It was pointed out that this type of device highlights the importance of careful clinical pathological coordination. Investigators should not assume that the muscle is normal in these patients, especially in diabetics where the smooth muscle can be damaged by fibrosis. Dr. McCallum stated that his group is doing full thickness biopsies and have not yet detected any damage in the smooth muscle of their patients.

### ***Where are the Gaps and Research Needs for Gastroparesis?***

Panka Jay Pasricha, M.D., Medical Branch Internal Medicine, University of Texas, Galveston, TX

Dr. Pasricha explained that study of gastroparesis is necessary because a huge unmet need exists, with a heavy burden of suffering that particularly affects young to middle-aged women. Unlike many chronic diseases, there is neither effective treatment nor effective palliation in a substantial portion of cases. Beyond the clinical burden, gastroparesis is also an important area to study because it may be the prototype for understanding disorders of the enteric nervous system. It would provide an opportunity to study structure-function relationships, gene plasticity, neuroimmune interactions, and neuroendocrine/CNS-ENS communication.

Beyond the gut and enteric nervous system this subject can also provide opportunities for understanding gastric emptying and gastric-brain axis in health and disease critical to understanding other diseases such as obesity, space and motion sickness, post-operative ileus, and neurodegenerative diseases of the CNS and PNS.

Dr. Pasricha stated that there are a number of general problems and barriers faced by researchers in the field of gastroparesis. Most clinical studies have been conducted in single centers with small numbers of participants, making it difficult to extrapolate data. Furthermore, many of the centers have referral biases, and it is unclear whether they can translate to the community. The lack of ready

access to biological material and few centers are able to handle the sophisticated processing required for meaningful insight has been a barrier for furthering a better understanding of etiopathogenesis. Knowledge of the pathophysiology of gastroparesis is hindered because nausea and others symptoms are poorly understood and difficult to study objectively, and understanding of gastric emptying remains incomplete.

The absence of systematic, prospective, long-term studies has made assessment of prognostic factors difficult, probably due to a reluctance of both patients and investigators to remain at a center long enough to gather longitudinal data useful for individual prognoses. Diagnostic and physiological testing requires refinement of the electrogastrogram so that it can provide information about the site of aberrant electrical activity and cellular basis of the abnormality. Although gastric emptying has been the gold standard for making this diagnosis, it correlates very poorly with symptoms. Other techniques are available, such as antroduodenal manometry; however, it provides limited information and is difficult procedure for both patients and physicians. Current approaches in treatment are largely empirical. There is a paucity of good prokinetic drugs, and there are few control trials on antiemetics being conducted.

Dr. Pasricha stated that probably the most common and most debilitating symptom associated with gastroparesis is nausea, yet it is also both medically and socially neglected. Prevalence rates in the general population approach 10%; however, the relationship of nausea in general to gastroparesis versus other functional upper GI disorders such as functional dyspepsia is unknown. In addition, the pathophysiology in upper GI motility disorders is fairly poorly understood, except that researchers have determined that it correlates poor-

ly with gastric emptying. Nor is the neurochemical and neuroanatomical substrate for nausea clearly understood which has led to a lack of effective treatment for the disorder.

In terms of existing themes and unanswered questions, Dr. Pasricha reminded the group that much discussion during the current meeting centered on the importance of neuronal NOS expression. However, investigators do not know whether it correlates in humans as it does in animal studies, do not understand the regulation of gastric neuronal NOS, and need to further examine the role of splice variants in health and disease.

Dr. Pasricha suggested that the animal models currently used (e.g., the nNOS knockouts and diabetic models) have a common problem in that some gross defects have been noted, but they have not been characterized pathophysiologically. Another complicating factor is that some seem to have a variable relationship or relevance to human diseases.

Further examination of nNOS regulation is also warranted. Although some work has been done in this area, the factors that regulate nNOS need to be better defined if researchers are going to use it as a model or a working paradigm in the study of gastroparesis. Splice variants have been shown to be expressed both in the stomach and throughout the GI tract, but the role of splice variants in health and disease states needs to be more thoroughly investigated.

Barriers to pathophysiology, structure, function, and pathophysiological relationships include a lack of knowledge of the relative role of pyloric versus antral/body dysfunction and the gastric region/defect correlation that best fits with individual symptoms. Targeting therapy in a meaningful way will require answers to questions such as these.

There is general consensus in the scientific community that the interstitial cell is a key player in the enteric system. However, more investigation in terms of cutaneous correlations is needed.

Questions regarding ICC loss and/or dysfunction and clinical consequences in terms of pathophysiology and symptomatology remain unanswered. Dr. Pasricha recommended that the pathogenesis be more closely studied on a molecular or ionic basis of gastric dysrhythmias, particularly the channels in the ICC that regulate rhythm. Gastric muscle affect has also been somewhat neglected in terms of investigations, as has the role of spinal afferents in regulating gastric emptying.

Emerging themes of study include roles of infection and inflammation in the enteric nervous system. Post-viral gastroparesis is believed to be an important subset of this patient population and is important both because there is a possible etiology and because it appears to have a more favorable prognosis. Correlation with human studies, investigation of the types of viruses that affect the ENS, immune response, and roles of other cells such as glial cells or resident macrophages, are also items of interest, and appropriate animal models do exist.

Morphological, physiological, molecular and neurochemical changes which occur in the vagus during gastroparesis (particularly nodose ganglia) need to be better understood, as does the role changes in the vagus play in symptomatology (especially nausea and, to some extent, pain).

The role of neuroendocrine mediators has been poorly studied in the clinical situation although there is a substantial amount of experimental evidence that hormones such as CCK, pancreatic polypeptide, and a long list of hormones do affect gastric emptying. The relationship between gastric emptying abnormalities, tissue energy stores and

the hypothalamic-satiety system requires attention, as does the role of entero-enteric reflexes and “field defects.”

Dr. Pasricha stated that existing techniques need to be evaluated for usefulness, including using the EGG to go beyond the slow wave and employing gastric electrical rhythms to stratify patients, providing more accurate prognoses and better clinical management. Vectorial methods electrical mapping may also be a beneficial tool.

Novel approaches should be developed to better understand gastric emptying in health and disease states, including gastric imaging (e.g., SPECT, MRI, and ultrasound) and functional brain techniques (e.g., distention, satiety, and nausea). Dr. Pasricha suggested that investigators take advantage of new techniques.

In terms of treatment, investigators need further insight into anti-nauseant drugs, and clinicians ought to seek out novel targets for prokinetics and determine how they can best be evaluated. Gastric electric stimulation and surgical treatment (including gastric decompression and partial gastrectomy) need to be better understood, and an optimal nutritional approach needs to be determined.

Given the limitations of knowledge in the area of gastroparesis, Dr. Pasricha remarked that a major barrier has been that there is not a large enough database of patients from which to glean answers. At the first meeting of the Gastroparesis International Task Force last year, it was proposed that a network of clinical research sites be created with central data collection and analysis to develop and implement common research protocols for the study of gastroparesis. Initial implementation would involve the acquisition of an initial epidemiological dataset relating natural history and disease

classification, followed by the establishment of one or two national repository sites to assess tissue, cell, and molecular pathogenesis. The repository sites would maintain a correlative pathological database and a serum bank would be established and maintained, providing a resource for investigators with specific questions.

The primary objective was to generate preliminary data and experience to enable the submission of several hypothesis-driven proposals to funding agencies. Secondary objectives were to develop a standard of clinical protocols for the diagnosis and management of gastroparesis patients. Once developed, the protocols would be used to educate gastroenterologists and community physicians. Protocols would also be developed for pathological examination of gastric tissue to study molecular and cellular mechanisms, as well as to illuminate genetic and environmental influences.

Dr. Pasricha identified a need for the development of further valid animal models to look at delayed gastric emptying and nausea. Multidisciplinary approaches using electrophysical, molecular, genomic and proteomic tools must be developed, and the peripheral (ENS), vagus, and central nervous systems warrant greater attention.

Sources for funding include traditional NIH-funding and technology-based research (such as SBIR, STTR, and DOD) for new physiological and diagnostic tests and better methods for gastric electric stimulation. Opportunities also exist for orphan product development in terms of looking at subsets of gastroparesis.

### **Discussion**

A participant asked for clarification of specific infections associated with gastroparesis, to which

Dr. McCallum responded that some patients experienced DMV, Epstein Barr, or rotovirus. Once the infection is discovered, it may be too late for rigorous testing in humans; however, it may be beneficial to create an animal model to study the process. Dr. Camilleri stated that sometimes the damage caused by viruses can be extrinsic, and biopsying the stomach may not provide enough answers.

### **Group Discussion: Future Research Directions**

**Facilitators:** Chung Owyang, M.D., Internal Medicine Department, University of Michigan, Ann Arbor, MI and Frank Hamilton, M.D., MPH, Chief, Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD

Dr. Owyang opened the discussion with a comment that the clinical problems investigators face in the field of gastroparesis will not be corrected quickly or easily, but will require extensive studies conducted in a logical, organized manner. An effective solution will be dependent upon improved mechanisms for data collection and analysis and follow-up of patients over an extended period of time. A central facility for tissue collection will be important for molecular studies, and appropriate animal models need to be developed. Funding is available, but is extremely limited compared to the magnitude of the problem. Dr. Owyang then opened the floor for discussion.

Dr. Sanders asked whether this type of plan fit the NIH Road Map concept, since it would be helpful to have some organization where different approaches and aspects could be brought together, since single investigators are not truly equipped to conduct this type of research.

Dr. James remarked that only modest progress has been made in the field, but that a tremendous range of opportunities remain. While individual investigators may not have the resources to take full advantage of nationally developed technological resources, the Road Map strategies were meant to look beyond individual diseases or institutes. Therefore, the initial RFAs that have come from the Road Map are not disease-specific. They are instead basic building blocks, such as technologies, proteomic platforms, informatics, metabolomics, and novel innovative imaging techniques that can be used by any clinician studying a complex disease. In terms of multidisciplinary science, a number of RFAs are designed to encourage the creation of novel groups of innovative individuals. Institutional impediments need to be eliminated, so that cooperation between investigators is both possible and encouraged.

Dr. James stated that the NIDDK has created a repository of serum, plasma, tissue, databases, DNA, cell lines, and more, which will be made available to all its current large multicenter clinical investigations. Congress has provided an additional \$150 million in funding for Type 1 diabetes research across NIH, and NIDDK is playing a role in the administration of those funds. Clinical trial programs and networks for Type 1 diabetes include TrialNet, which will be able to reposit samples. A new program is being implemented in conjunction with NCI to allow investigators in Type 1 diabetes to develop novel therapeutic approaches.

As an example of methods being undertaken to satisfy unmet clinical needs, Dr. James described the Type 1 Diabetes RAID Program, which will allow applicants to develop in-house and move through phase 1 clinical trials, including all the steps required for drug development. In addition, a new program announcement was recently released

which will aid investigators in the development of high throughput screens. NIH has an initiative to develop a molecular library which will not have the constraints of a pharmaceutical company. As more animal models that are developed, more investigators will be brought into the field from other areas. Those models will become the foundation for testing new hypotheses, potential agents, and biological agents.

NIH would like to help develop a clinical network, but funds are limited. Instead, Dr. James suggested that the clinicians in the field of gastroparesis consider examples of other groups of highly motivated individuals that have put together consortia and cohort studies.

Dr. James also emphasized the importance of bringing new and younger investigators into the field and calling on physicians to be mentors and trainers. Various career development awards are available and should be promoted so that the field will have the benefit of greater numbers of well-trained investigators in the future.

The issue was raised that the development of an atypical RFA for a distributive center where individuals could work together on a problem might be an interesting avenue around limited funding. Dr. James responded that approximately 12 cooperative agreement projects are currently being funded under the U series grants, with NIH playing an active role in supervising the projects, usually through a steering committee for each of the centers. The same goal can be accomplished with large projects involving many centers that are an R01 where a group has decided to organize itself and create this type of entity, but where the investigators have done all the work. Beyond that, NIH is looking at better ways to try to encourage this type of activity through new kinds of grants.

Dr. James was asked if NIDDK has a procedure for prioritizing proposals in terms of those areas that have obviously significant morbidity and are traditionally underfunded. Dr. James answered that oftentimes there are huge disparities between the burden of illness and the number of grants that are funded. In some areas, there are important scientific opportunities that are ripe for investigation because research tools are available and reasonable hypotheses have been proposed. Grant requests at NIH are put through a peer review system with individuals who examine applications to decide the right ones to fund. It is definitely not a formulaic approach where a portion of the budget is allocated to funding research in a particular disease. There is some flexibility in terms of RFAs, but that is often determined by the availability of funds. When funding agencies are unsure of the right course of action, they hold workshops or meetings to bring both experts in the field and outside of it to collect ideas about how to accelerate progress. On the other hand, when it is clear that progress is being made, the NIH holds consensus conferences to get discoveries translated into practice in the community.

The field of gastroparesis is at a middle stage of the process in that it has not significantly impacted the patient, and yet there are a lot of exciting scientific opportunities. Probably the most important issue from Dr. James' point of view is to encourage more to funding research in a particular disease. There is some flexibility in terms of RFAs, but that is often determined by the availability of funds. When funding agencies are unsure of the right course of action, they hold workshops or meetings to bring both experts in the field and outside of it to collect ideas about how to accelerate progress. On the other hand, when it is clear that progress is being made, the NIH holds consensus conferences to get discoveries translated into practice in the community. The field of gastroparesis is at a middle stage of the

process in that it has not significantly impacted the patient, and yet there are a lot of exciting scientific opportunities. Probably the most important issue from Dr. James' point of view is to encourage more people to write more grants that are relevant to this area, or to bring in people who are involved in endeavors that might be relevant but have not necessarily been connected to the field thus far.

Dr. Pasricha stated that it is incumbent upon all those present and the society to encourage more people to become involved in submitting grant applications. Secondly, he pointed out that the field of gastroparesis is not one with many young investigators. His sentiment was echoed by another participant, who stated that this is a crucial role that needs to be catalyzed by professional societies, and who defined a successful meeting as one from which two or three new applications arise or where collaborations develop between individuals who have never worked together before.

In response to a question regarding the level of priority afforded funding for motility, Dr. James said that given the current status, there are opportunities for translating fundamental science into benefit for health problems, and certainly gastroparesis qualifies as an important health problem and the NIH would welcome additional grant applications. A short discussion followed regarding the review process, including peer review and study section processes. Dr. James concluded the meeting with an offer to provide website addresses for sites that outline and post available RFAs for obesity research, and the meeting was adjourned.

## Review of the Trans-NIH Action Plan for Liver Disease Research

June 15, 2004  
 Room 701, Two Democracy Plaza  
 6707 Democracy Boulevard  
 Bethesda, Maryland

### I. ATTENDEES

#### ***Liver Disease Subcommittee (LDS)***

##### **Chair:**

Jay H. Hoofnagle, MD, NIDDK

##### **Members:**

James Everhart, MD, NIDDK  
 Stephen James, MD, NIDDK  
 Leslye Johnson, PhD, NIAID  
 Thomas Kresina, PhD, NIDA  
 Qi-Ying Liu, MD, NCCAM  
 Aron Primack, MD, FIC  
 Tonse Raju, MD, DCH, NICHD  
 Jose Serrano, MD, PhD, NIDDK  
 Carol Shreffler, PhD, NIEHS  
 David Wilde, MD, PhD, NCRR  
 Sam Zakhari, PhD, NIAAA

#### **Other Members of the Digestive Diseases Interagency Coordinating Committee (DDICC):**

Vishnudutt Purohit, PhD, NIAAA

##### **Other Participants:**

Patrick Donohue, PhD, NIDDK  
 Edward Doo, MD, NIDDK  
 Richard Farishian, PhD, NIDDK  
 Megan Miller, PhD, NIDDK  
 Lopa Mishra, MD, Veterans Affairs Medical Center,  
 Washington DC  
 Griffin Rodgers, MD, NIDDK

### II. OVERVIEW

#### ***A. Welcome and Overview of the Development of the Trans-NIH Action Plan for Liver Disease Research—Dr. Hoofnagle***

The draft Action Plan for Liver Disease Research has been developed over the past months through the efforts of several groups, including the Liver Disease Research Branch of the NIDDK, members of the Liver Disease Subcommittee of the DDICC, the intramural and extramural research communities, and lay and patient advocacy groups, with oversight by the LDS/DDICC. To date, approximately 200 individuals, mostly from outside the NIH, have been involved in developing the content of the Action Plan. After creation of an outline and structure for the Action Plan, in which liver disease research was divided into 16 topic areas, an assessment of current NIH support of liver disease research was conducted to provide an information base for the Action Plan and to identify NIH Institutes and Centers (ICs) that should participate in its development. Sixteen Working Groups (WGs) were formed with six to eight individuals from the extramural and intramural research communities and patient advocacy groups to cover each topic area. The assessment of current NIH support for liver disease research yielded information on levels of funding for each of the

topic areas, with some consolidation of areas (e.g., inclusion of support for basic research and liver disease in HIV-positive persons within the viral hepatitis category). Viral hepatitis and liver cancer were highlighted as areas of large, disease-focused investment in liver disease research by the NIH.

After the WGs contributed content for the Action Plan chapters via email and teleconference, drafts of the Action Plan chapters were prepared through the following process: (1) first drafts of the Action Plan chapters were written by members of the Liver Disease Research Branch, NIDDK, and were then distributed to the appropriate WG for review; (2) a second draft of each chapter was then sent to a group of primary reviewers, composed of members of the extramural and intramural research communities and patient advocacy community; (3) the reviewers' comments were addressed (third draft); then (4) drafts were prepared for posting on the Action Plan website ([http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb\\_action\\_plan.htm](http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb_action_plan.htm)). Currently, three chapters are at the first draft stage, eight chapters are at the second draft stage, one chapter is at the third draft stage, and four draft chapters have been posted to the website. In Summer 2004, the final drafts of all Action Plan chapters will be posted to the website, and the website will be used to invite input from the broader community of liver disease researchers and lay individuals during an approximately 1-month period. The Action Plan will be completed in early Fall 2004.

The Action Plan is focused on important and representative research goals, with an emphasis on translational research. Goals were identified that were neither too specific nor too broad and that should be measurable for future evaluation of these efforts. Each WG used a 3x3 matrix

(modeled after the matrix used by Dr. Zerhouni, NIH Director, to set research goals for the NIH under the Government Performance and Results Act) to develop clear research goals and classify them as short-, intermediate-, or long-term, and as low-, medium-, or high-risk (in terms of degree of difficulty in attainment). In addition to the research goals presented in text and matrix forms, the Action Plan chapters developed by the WGs include background information and recent research advances in the topic area, as well as a section on steps needed to achieve research goals. The latter section on steps to achieve research goals will be a critical focus for the Liver Disease Subcommittee (LDS), as this content describes potential NIH mechanisms to attain the research goals. The Action Plan chapters will be complemented by introductory and concluding sections, including a list of recommendations and a "top 10" list of overarching themes for research goals across the Action Plan.

### III. OPEN DISCUSSION

#### ***A. General Comments on the Chapters of the Trans-NIH Action Plan for Liver Disease Research***

The group first discussed how best to integrate into the Action Plan topics important to liver disease research that are currently absent, including international research, minority health issues, women's health issues, complementary and alternative medicine, training, and utilizing knowledge gained through the Human Genome Project and the Human Proteome Project. Several of these topics cut across many areas of liver disease research and will be included in the introductory or concluding sections of the Action Plan.

## 1. International Research

The international component of liver disease research is important to include in the Action Plan, in part because certain liver diseases are so prevalent worldwide. Diseases such as hepatitis B and liver cancer are easier to study in countries outside of the U.S. because research can be conducted more efficiently due to the capability to recruit more people and conduct research at a lower cost than is possible within the U.S. International research also benefits from the unique cultural differences in disease factors encountered worldwide, such as diet, alcohol use, and prevalence of infectious disease. Although the benefit of international research to the NIH and to the U.S. population is sometimes questioned, research on infectious liver diseases that spread to the U.S. and on pathology of liver diseases that significantly affect the U.S. population is obviously worthwhile.

International research on liver disease is currently supported by some ICs of the NIH. Liver disease research training and research supported through the Fogarty International Center (FIC) is being conducted as a collaboration between U.S. institutions that train researchers and foreign sites where the research is actually conducted. The combination of U.S. research resources (to support such items as equipment for sample processing and analysis) and foreign sites has been effective. The FIC often uses the D43 training mechanism and K awards to support these efforts. Also, the Fogarty International Research Collaborative Award (FIRCA) program expands current NIH-supported research programs to the international setting, including the developing world, which is a site of much of this research. FIRCA ensures that the U.S. and the participating country each derive some benefit from the research. An NIAID-supported study in Egypt was also provided as an example of utilizing a foreign site to

recruit research patients. Gallbladder disease/biliary cancer research and obesity/nonalcoholic steatohepatitis (NASH) are examples of liver/biliary diseases of importance to the U.S. population that could be effectively researched in other countries. It was suggested that international issues be dispersed throughout the Action Plan by identifying types of future research projects on such topics as hepatitis research, which could be conducted abroad with potential benefits for both the foreign countries and the U.S.

## 2. Minority and Women's Health Issues

Women are more susceptible to or more affected by some types of liver disease. For example, women are more susceptible to liver damage due to alcohol abuse. Autoimmune liver diseases are more prevalent in women. Liver disease during pregnancy is also an important issue and should be included in the Action Plan; input will be sought from NICHD staff who cover this area.

Regarding minority health issues, it was noted that some minority groups in the U.S. are more susceptible to or affected by certain liver diseases. For example, Asian Americans are generally more susceptible to alcohol-induced liver damage. American Indians are also at increased risk of liver disease. The death rate for liver disease is highest for American Indians, followed by Hispanic whites; the rates for African Americans and Caucasians are lower and roughly equivalent. Hispanics, especially Mexicans and Central Americans, are more susceptible to nonalcoholic steatohepatitis (NASH), which occurs at a lower body mass index and is more severe in this group, suggesting that indigenous admixture may be an important factor in etiology. It might be useful to research the prevalence of liver disease in Hispanics who reside outside of the U.S. in order to compare that rate to the prevalence

within the U.S. However, care should be taken when comparing liver disease prevalence across countries because of differences in diet, lifestyle, and other confounding factors; for example, in Mexico, some alcohol is contaminated with lipopolysaccharide, which causes liver damage and cirrhosis.

Subcommittee members were requested to send Dr. Hoofnagle examples of liver diseases which are more prevalent or severe in a gender or minority group so that these concepts can be considered for inclusion in the Action Plan.

### **3. Complementary and Alternative Medicine (CAM)**

Information about several CAM substances (e.g., S-adenosylmethionine, silymarin) has been included in the fatty liver disease chapter. The chapter on drug-induced liver disease may be the appropriate place to further emphasize CAM treatments, especially in terms of the ways in which these therapies interact with drugs and can lead to drug-induced hepatotoxicity.

### **4. Research Training**

A large Request for Applications (RFA) is currently open for K-12 applications to train clinical researchers in translational research using a multi-directional approach, to piggyback on the K-30 award program. Typically, such applications support training in areas for which research funding is already available, rather than for areas that have a dearth of such financial support; this problem is especially acute for drug-induced liver disease because of the lack of clinical research in that area. The challenge will be to provide training grants in research areas that are not now well represented in the research community.

### **5. Human Genome and Proteome Projects**

The Human Genome Project, supported by the National Human Genome Research Institute, and the Human Proteome Project, an international effort, are relevant to all sections of the Action Plan. The Introduction to the Plan could describe how these efforts relate to the Action Plan and to the topics covered in the chapters. For example, small molecules to study such issues as hepatocyte polarity, liver disease detection, or therapy could be described within a section of the Introduction on nanotechnology.

These and other areas of liver disease research could benefit from the development of high-end instrumentation through a shared instrumentation program among researchers, such as a program supported by the National Center for Research Resources. Proteomics could benefit from a shared resources approach, as could various imaging techniques; for example, imaging techniques to detect hepatocellular carcinoma early in mouse models would be a significant asset. Shared informatics might also be useful.

### ***B. Comments on Specific Chapters***

Dr. Hoofnagle reviewed the major goals identified by each Working Group (WG) within their respective chapters. He requested that each of the IC representatives on the Liver Disease Subcommittee/DDICC review the chapters and send their comments by email.

#### **WG 1a. Cell & Molecular Biology of the Liver**

This chapter focuses on trafficking and membrane transporters, cell polarity, cellular interactions, and the unique structure of the liver. One of the research goals identified by the WG is to duplicate

the liver structure in a cell culture system that replicates the cellular interactions that occur in vivo.

### **WG 1b. Liver Injury, Repair, Fibrosis, & Inflammation**

This chapter covers a significant portion of the NIH research portfolio in liver disease. The major research goals identified by the WG are in the areas of apoptosis and anti-apoptosis therapies; fibrosis and anti-fibrosis therapies; biomarkers; proteomic analysis of the response to injury or fibrosis; the innate and adaptive immune system and the liver; liver and inflammation; and genetic determinants of disease progression.

### **WG 1c. Developmental Biology & Regeneration**

The broad goal initially identified by this WG was to define the molecular and cellular steps involved with liver regeneration, differentiation of regenerative cells to mature hepatocytes, and organogenesis, which was narrowed down to a few specific and measurable research goals. Specific research goals developed for the chapter included the development of gene therapy for metabolic liver disease; identification of biomarkers to monitor regeneration in such conditions as acute liver failure and post-transplantation; and the identification of therapies that promote regeneration.

### **WG 1d. Bile, Bilirubin, & Cholestasis**

General goals in this area outlined in the chapter include more fully defining the plasma membrane transporters of bile and bile acids, cholesterol, and lipids. The translational issues identified include defining intrahepatic cholestatic liver disease on a molecular basis and developing gene therapies for syndromes in which a transporter or enzyme is deficient.

### **WG 2. Viral Hepatitis**

One of the areas receiving much attention in viral hepatitis is the role of the innate immune system in determining the outcome of the disease—particularly the early immune responses that occur during the course of acute hepatitis B and C. Research goals identified in this area by the WG include: developing better cell culture systems for hepatitis viruses (particularly for hepatitis C); understanding the stability of hepatitis B virus DNA, which has impeded efforts to eradicate the virus; developing a hepatitis C vaccine and an improved, possibly single injection, hepatitis B vaccine for use in developing countries and immunocompromised patients; and developing improved therapies for viral hepatitis.

### **WG 2e. HIV & Liver Disease**

This chapter deals with liver diseases that frequently affect HIV-infected persons, including viral hepatitis, fatty liver disease, and drug-induced liver injury. Specific research goals include defining the interactions between HIV and the hepatitis viruses; the etiology of fatty liver disease in HIV-positive patients; and reactivation of hepatitis B. This chapter has emphasized international research because rates of liver disease are expected to rise with the introduction of antiretroviral therapy into the developing world to treat HIV infection.

### **WG 3. Fatty Liver Disease**

Research goals in this chapter include developing and testing therapies for alcoholic and nonalcoholic fatty liver disease in clinical trials. Another major research goal identified by the WG is to address the need for animal models of fatty liver disease, particularly of NASH, as no model currently replicates the disease in terms of chronicity, progression, and fibrosis. Other research goals identified by the WG

are to establish cohort studies of the natural history of NASH—with particular attention to genetic factors that predispose to the development of fibrosis—and to develop noninvasive biomarkers, which, by indicating the pathogenesis of NASH, might lead to useful targets for therapy.

#### **WG 4. Drug- and Toxicant-Induced Liver Disease**

Research goals identified by the WG in this chapter include: (1) developing in vitro and in vivo models for hepatotoxicity, particularly idiosyncratic hepatotoxicity, (2) identifying the chemical substructures that lead to liver toxicity, (3) developing improved methods to establish and grade causality, (4) defining the incidence of hepatotoxicity in the U.S., and (5) characterizing the role of the innate immune system in idiosyncratic drug-induced injury and the adaptive response. Additional content on the subject of complementary and alternative medicines (CAMs) could be included in this chapter, as noted previously (see section III.A.3.).

One of the challenges is determining how to collaborate with industry in the study of drug-induced liver disease. Industry conducts a significant amount of this research, but much of the resulting information and tools are proprietary; for example, animal models are not shared with the non-industry research community. To address these concerns, the WG suggested regular scientific meetings that include researchers from industry, academia, and government to foster collaboration in addressing common research goals. It was also suggested that drug companies be asked about gaps in liver disease research that they are not currently studying and that industry's attention be called to the Action Plan draft during the public comment period.

#### **WG 5. Autoimmune Liver Disease**

Autoimmune liver disease includes primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), and autoimmune hepatitis. Few NIH grants currently support research in this area. The WG determined that animal models of each of these diseases are needed, and suggested a meeting on this topic involving groups that deal with other autoimmune diseases and have been successful at developing animal models. Other research goals include defining genetic factors and biomarkers for autoimmune liver diseases.

#### **WG 6. Pediatric Liver Disease**

Research goals identified by this WG include research on the molecular basis and the developmental biology of pediatric liver diseases, including biliary atresia, metabolic disorders, intrahepatic cholestatic disorders, Alagille syndrome, Wilson disease, and viral hepatitis. The group also emphasized that nomenclature used to classify and describe pediatric liver disease should be standardized to assist in diagnosis and treatment.

#### **WG 7. Genetic Liver Disease**

This chapter focuses primarily on hemochromatosis, Wilson disease, and porphyria. In the case of hemochromatosis, the genetic defect underlying the majority of cases has been identified, but this finding does not account for iron overload in many populations, such as in persons of African or Asian descent. Therefore, identifying the molecular basis of hemochromatosis in these patient populations is an important goal. Other goals include developing a means of screening for hemochromatosis; defining the role of iron in other liver disease; developing a

blood test usable at birth that identifies Wilson disease; and developing gene or stem cell based therapy for certain forms of porphyria.

### **WG 8. Liver Transplantation**

Research goals identified by the WG include identifying biomarkers of acute cellular rejection and understanding the basis of immune tolerance post-transplantation. The two major challenges identified in the area of liver transplantation are the availability of organs (more than 1,000 Americans die each year while waiting for a liver), and effectively maintaining the long-term health of people who have a liver transplant. Because the best way to ensure long-term health post-transplantation currently is to remove transplant recipients from immunosuppression and hope that they retain immune tolerance, three important goals are to identify: (1) the mechanisms of immune tolerance; (2) how to promote immune tolerance; and (3) how to identify the person who is immune tolerant and could be withdrawn from immunosuppression.

### **WG 9. Complications of Liver Disease**

Several clinical research goals were put forth by the WG for this chapter, and underlying many of those goals is the need to better understand the pathophysiology of portal hypertension and to find better drugs to treat it. Research goals include determining how to lower portal pressure based on pathophysiology and whether molecular targets can be identified and small molecules developed to treat portal hypertension at its various stages.

### **WG 10. Liver Cancer**

Based on the fact that hepatocellular carcinoma (HCC) accounts for approximately 90 percent of liver cancer in the U.S., the WG dealt primarily with

HCC and not with cholangiocarcinoma or hepatoblastoma. Research goals identified included the development of molecular targets and biomarkers, and a tissue bank and better surveillance system for this type of cancer in the U.S. (the National Cancer Institute has mechanisms to accomplish these goals). Standardization of nomenclature used to diagnose HCC is also a research goal.

### **WG 11. Gallbladder & Biliary Disease**

Research goals identified by the WG include the development of better imaging methods for the biliary tree; development of biomarkers for lithogenic bile; definition of the role of bacteria in causing cholesterol gallstones and biliary pain; and characterization of the genes that appear to underlie susceptibility to cholesterol gallstones.

### **WG 12. Liver Imaging & Biotechnology**

Research goals identified by the WG are focused primarily on molecular imaging of the liver. Specific goals include developing an online database correlating liver tissue samples with imaging results; developing better imaging methods to quantify fat, fibrosis, and inflammation in the liver using molecular markers; and bioinformatics resources to integrate imaging technologies.

## **IV. WAYS TO INVITE BROADER PUBLIC INPUT (GRANTEES, ACADEMIC SOCIETIES, LAY GROUPS)**

The group discussed ways to inform additional individuals interested in liver disease research about the draft of the Action Plan to be posted on the website in the coming months and to invite their comments on the draft. Potential avenues to accomplish this include mass emails to: (1) grantees

of the Subcommittee members' ICs; (2) representatives of academic groups (e.g., American Association for the Study of Liver Diseases; North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; American Gastroenterological Association; and other constituency groups of the Subcommittee/Committee members' ICs or agencies); (3) representatives of lay groups (e.g., American Liver Foundation; Hepatitis Foundation International; and other constituency groups of the Subcommittee/Committee members' ICs or agencies); and (4) industry representatives. These individuals would be encouraged to access and review the draft Action Plan posted on the website and to submit their comments to an email address provided on the website.

When the draft Action Plan is posted, staff of the Liver Disease Research Branch/NIDDK will distribute email templates to the Subcommittee members to tailor and send to their grantees and constituency groups. These email templates will include a description of the Action Plan, a link to the website on which it is posted, and an invitation to review sections that pertain to the reviewer's areas of interest and expertise.

## **V. IDEAS FOR SUMMARY RECOMMENDATIONS**

The concluding section of the Action Plan will include a "top 10" list of major goals that encompass several of the topic areas. The group discussed a preliminary list, which will be finalized after the chapters reach the final draft stage. Recurring themes from the WGs include the development of biomarkers; standardization of nomenclature; improving outcomes of living donor liver transplantation; ways to address the increase in the mortality rate for liver disease; and development of a hepatitis C vaccine.

## **VI. COMPLETION OF THE ACTION PLAN DOCUMENT**

Each Subcommittee member was requested to look through the Action Plan document for the chapters that pertain to his or her IC's portfolio and to email comments to Dr. Hoofnagle. It is anticipated that one month will be provided for public comment prior to completion and publication of the Action Plan in hard copy and in electronic form on the website. Comments from Subcommittee/DDICC members will be welcome at any time.

## **VII. IDEAS FOR FIRST STEPS TO IMPLEMENT THE ACTION PLAN**

Plans to implement some of the goals of the Action Plan are already being considered, which will be finalized when the Action Plan is completed. For example, the genetic liver disease WG suggested the formation of a central database for porphyria gene sequencing, data collection, and to provide a focus for the research community. Research responsibility for porphyria transcends NIDDK divisions (Division of Kidney, Urologic, and Hematologic Diseases, and Division of Digestive Diseases and Nutrition) and the National Heart, Lung, and Blood Institute. Because this disease is rare, it may be appropriate to approach the Office of Rare Diseases about developing a working group on porphyria, with a possible meeting of the LDS on porphyria in Fall 2004. Subcommittee/DDICC members are encouraged to identify ways to implement the Action Plan and to share these ideas with Dr. Hoofnagle.

## VIII. MISCELLANEOUS

A request was made that Dr. Hoofnagle make his slides available following the meeting. Dr. Hoofnagle will email a modified version of his slides to the Liver Disease Subcommittee/DDICC.

## IX. ADJOURNMENT

Dr. Hoofnagle adjourned the meeting at 3:30 PM.

*Reference:* The final version of the completed Action Plan is available at the NIDDK website:  
[http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb\\_action\\_plan.htm](http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb_action_plan.htm)

## Appendix I

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## Appendix III

### ACRONYMS LIST

<b>CAM</b>	complementary and alternative medicine	<b>NIBIB</b>	National Institute of Biomedical Imaging and Bioengineering
<b>CSR</b>	Center for Scientific Review	<b>NICHD</b>	National Institute of Child Health and Human Development
<b>DDICC</b>	Digestive Diseases Interagency Coordinating Committee	<b>NIDA</b>	National Institute on Drug Abuse
<b>FDA</b>	U.S. Food and Drug Administration	<b>NIDDK</b>	National Institute of Diabetes and Digestive and Kidney Diseases
<b>FIC</b>	Fogarty International Center	<b>NIEHS</b>	National Institute of Environmental Health Sciences
<b>FIRCA</b>	Fogarty International Research Collaborative Award	<b>NIGMS</b>	National Institute of General Medical Sciences
<b>ICs</b>	Institutes and Centers	<b>NIH</b>	National Institutes of Health
<b>LDS</b>	Liver Disease Subcommittee	<b>NINR</b>	National Institute of Nursing Research
<b>NASH</b>	nonalcoholic steatohepatitis	<b>NLM</b>	National Library of Medicine
<b>NCCAM</b>	National Center for Complementary and Alternative Medicine	<b>PBC</b>	primary biliary cirrhosis
<b>NCI</b>	National Cancer Institute	<b>PSC</b>	primary sclerosing cholangitis
<b>NCRR</b>	National Center for Research Resources	<b>RFA</b>	Request for Applications
<b>NHGRI</b>	National Human Genome Research Institute	<b>WG</b>	Working Group
<b>NHLBI</b>	National Heart, Lung, and Blood Institute		
<b>NIAAA</b>	National Institute on Alcohol Abuse and Alcoholism		
<b>NIAID</b>	National Institute of Allergy and Infectious Diseases		

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