Testimony Before the
Committee on Government Reform
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"STALKING A FURTIVE KILLER: A REVIEW OF THE FEDERAL GOVERNMENT'S EFFORTS TO COMBAT HEPATITIS C"

Statement of

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Mr. Chairman and Members of the Committee: I am Jay Hoofnagle, Director of the Liver Disease Research Branch in the Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This is the Institute that has major responsibility for hepatitis C research at the National Institutes of Health (NIH) of the Department of Health and Human Services (HHS). I am pleased to testify today regarding NIH efforts to combat hepatitis C infection. Through basic and clinical research studies, we can gain greater insights into the diagnosis of hepatitis C, find more effective treatments, and develop prevention strategies.

At the NIH, hepatitis C is a shared research focus of the NIDDK, the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and the National Heart, Lung, and Blood Institute (NHLBI). In my testimony today, I will give you a brief overview of the public health burden of hepatitis C, the current status of research, planning, and coordination of efforts at the NIH, and our major goals for future research.

It is particularly appropriate for this Committee to have a hearing at this time on this topic. The hepatitis C virus was discovered just 15 years ago. Yet, today it is clear that hepatitis C is the most common cause of chronic liver disease in the United States, the most common cause of liver cirrhosis, the most common indication for liver transplantation, and now the most common cause of liver cancer. Hepatitis C is, thus, the most critical area of all liver disease research.

Hepatitis C research is particularly important for another reason. Hepatitis C is caused by a virus; and as such, this disease is treatable and potentially preventable. Control of this viral infection would eliminate the most common cause of cirrhosis in our country. Furthermore, recent research on hepatitis C has provided new tools that may make the control and prevention of this disease a practical reality, leading to decreases in the burden of this chronic liver disease, and bringing immediate and tangible benefits to large numbers of people.

OVERVIEW OF HEPATITIS C

The hepatitis C virus (HCV) is a pathogenic infectious agent that causes a major form of hepatitis, or liver inflammation, in humans. HCV is spread mainly through contact with infected blood and blood products. Currently, the main source of HCV transmission in the U.S. is through the use of shared, unsterilized needles, syringes, and other drug paraphernalia among injection drug users. Transmission of HCV through blood transfusions, historically an important cause of transmission, has been largely eliminated in recent years due to routine screening of the blood supply for the virus. Sexual spread of hepatitis C occurs, but is not common.

Population surveys indicate that approximately 4 million Americans have been infected with HCV, of whom 3 million have chronic infection with the hepatitis C virus; the majority of these individuals are probably unaware of having this disease. Acute hepatitis C is uncommonly recognized because it is usually silent and not associated with symptoms or signs of liver disease. The greater health threat posed by hepatitis C virus infection is that the acute infection fails to resolve in most instances, and the disease advances to chronic hepatitis C, which may progress further to cirrhosis, potentially leading to liver failure, and even to liver cancer.

Not all patients with chronic hepatitis C virus infection develop severe liver disease. Furthermore, progression of liver disease is typically slow. Thus, approximately 10 percent of persons with hepatitis C virus infection develop cirrhosis per decade of infection. Liver cancer generally arises only after cirrhosis has been present for many years, at an annual rate of 1 to 3 percent per year. For these reasons, therapy of hepatitis C is generally recommended mainly for persons who have evidence of progressive liver disease.

Chronic hepatitis C is the most common reason for liver transplantation in the U.S., and results in an estimated 8,000 to 10,000 deaths each year in this country. The burden placed on the U.S. healthcare and economic systems by chronic hepatitis C is also great, estimated at $758 million spent in 2000 on medical costs and lost work hours due to the disease (Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, Gemmen E, Shah S, Avdic

A, Rubin R. The burden of selected digestive diseases in the United States. *Gastroenterology* 2002 May;122(5):1500-11).

CURRENT STATUS OF RESEARCH ON HEPATITIS C

What is the current status of research on hepatitis C? I will discuss 3 areas: diagnosis, treatment, and prevention.

Diagnosis and evaluation: There are now accurate tests to diagnose hepatitis C infection. These are widely used and have been critical in screening of blood donors. The introduction of tests for hepatitis C has led to the disappearance of post-transfusion hepatitis and improvement in the safety of our blood supply. In 2000, Dr. Harvey Alter of the NIH Department of Transfusion Medicine at the NIH Clinical Center and Dr. Michael Houghton of the Chiron Corporation were awarded the prestigious Lasker Award for their contributions to the discovery of the hepatitis C virus and development of means of testing blood to eliminate post-transfusion hepatitis C. While diagnosis of hepatitis C is now reasonably straightforward, evaluation of patients for the degree and stage of liver injury is still difficult and inaccurate, relying upon liver biopsy and x-rays. Research is being focused on developing accurate means of assessing liver disease in persons with hepatitis C.

Treatment: There are improved means of treatment of hepatitis C. The initially approved therapy for hepatitis C was a 6- or 12-month course of treatment with standard interferon alfa. This therapy, however, resulted in sustained benefit in fewer than 20 percent of patients (1 in 5). Fortunately, in the last five years, therapy of hepatitis C has advanced, first with the introduction of the antiviral agent ribavirin and second with the development of an improved, long-acting interferon, called peginterferon. The currently recommended regimen of a combination of peginterferon and ribavirin results in sustained benefit in approximately 50 to 55 percent of persons with hepatitis C. In fact, among patients with certain strains of virus (called genotypes 2 and 3), response rates are greater than 80 percent. In addition, the response in persons with hepatitis C has now been shown to be more than a temporary improvement. A sustained response has been shown to be a complete eradication of the virus

from the liver and cure of the chronic infection. These advances in treatment of hepatitis C have been heartening, but we are working to achieve even better progress.

Prevention: Prevention of hepatitis C has been an area of special focus of research, but one of limited progress to date. Actually, the discovery of the hepatitis C virus and introduction of HCV testing was followed by an immediate and marked drop in the incidence of new cases of hepatitis C in the United States. Between the mid-1980s and 1995, the estimated number of new hepatitis C infections fell by 80 percent, but has remained relatively constant since 1995 at about 30,000 per year. Further progress in prevention, however, awaits advances in developing a specific means of prevention, such as an HCV vaccine. Work on this is ongoing, but the development of such a vaccine has been difficult. Unlike hepatitis A or B, antibodies to hepatitis C do not lead to recovery and fail to prevent infection even when present in high levels. Indeed, persons who recover from hepatitis C, either spontaneously or as a result of therapy, remain susceptible to re-infection. Thus, the conventional means of vaccine development have not been successful in hepatitis C and new approaches are being investigated.

CURRENT PROGRAMS, PLANNING, AND COORDINATION OF EFFORTS IN HEPATITIS C RESEARCH AT THE NIH

The NIH conducts, supports, plans, and coordinates hepatitis C research in a number of ways. First and foremost, the NIH supports a solid, ongoing portfolio of investigator-initiated hepatitis C research grants that are funded based on scientific merit as judged by the peer review system. To complement this investigator-initiated research, NIH Institutes and Centers initiate and propel research solicitations, scientific conferences, workshops, and public education. While hepatitis C research is pursued by multiple Institutes, there are mechanisms in place to assure coordination among the Institutes and Centers in the funding of research grants, research centers, and clinical trials. The Institutes and Centers work together under the auspices of a trans-NIH Hepatitis C Working Group to develop new initiatives, requests for applications, and ideas for workshops and symposia.

For fiscal year 2004, hepatitis C research was funded at a level of $118 million NIH-wide, the largest amounts of which came from the NIAID, NIDDK, NCI, NIDA, NIAAA, and NHLBI. Funding has risen markedly in the last few years, fueled by the recent doubling of the NIH budget as provided by the Congress and Administration. Let me point out that during this overall doubling of the NIH budget, funding for hepatitis C increased nearly five-fold, demonstrating the relative and emerging importance of research into this disease. Hepatitis C has been an area of high priority to the NIH during this critical period of our budget doubling.

In building the hepatitis C research portfolio, we recognize the importance of input from the scientific and lay community external to the NIH. I would like to provide just a few examples. One example of input that guides NIH program development can be found in the insights and recommendations we obtain from a wide range of conferences and workshops. For example, the NIH has sponsored critically important Consensus Development Conferences on hepatitis C in 1997 and 2002, and last spring we submitted to the Congress a report on our implementation of the recommendations we received from the 2002 Conference. The Conference was organized by the NIDDK in collaboration with the NIH Office for Medical Applications of Research and seven other NIH Institutes. Other participating Federal agencies or Centers included the Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration, the Health Resources and Services Administration, and the Centers for Medicare and Medicaid Services within HHS; the U.S. Department of Veterans Affairs; and the Office of the Assistant Secretary of Defense. The proceedings of the Conference were published in the November 2002 issue of the journal *Hepatology* (Vol. 36 (5), Supplement 1; available at: http://consensus.nih.gov/cons/116/116cdc_intro.htm).

Consensus Development Conferences are a source of valuable information to help guide research directions at the NIH. The two Conferences on hepatitis C provided an overview of the current understanding of its cause, natural history, complications, prevention, and treatment. The statements of the Consensus Development Conference Panels also provide objective, evidence-based recommendations on the clinical management of this disease. In addition, the Panels were asked to develop a list of important areas for future research that would help improve the management of hepatitis C. These suggestions have been used to inform initiatives developed by the NIH and other Federal agencies.

Recent initiatives in hepatitis C spearheaded by the NIH relevant to important areas for future research identified by the 2002 Consensus Conference Panel include:

- $ A large, multi-institute supported RFA on "Hepatitis C: Natural History, Pathogenesis, Therapy, and Prevention" published in January 2003, that encouraged research project applications in the areas that were outlined in the recommendations from the Consensus Development Conference. Six Institutes participated in this RFA. Twenty-nine applications were supported that will help to advance the field of research on hepatitis C management.
- $ Several NIH workshops have addressed specific issues raised in the Consensus Conference, including "Hepatitis C and Renal Disease," "Hepatitis C in Prison Populations," "Hepatitis C and Substance Abuse," "Hepatitis C and the Brain," and "Hepatocellular Carcinoma: Screening, Diagnosis and Management." Several more workshops are planned, for example, on the subjects of alcohol and hepatitis C, and hepatitis C vaccines.
- $ Several clinical trials and networks in hepatitis C have been established, both *de novo* and as a part of existing clinical trial consortia, including studies of patients with advanced liver disease (HALT-C trial), African Americans with chronic hepatitis C (Virahep-C trial), liver transplant patients (A2ALL trial), patients with HIV infection (Adult AIDS Clinical Trials Group or AACTG), and children with chronic hepatitis C (Peds-C trial). Furthermore, pilot studies are presently in development to address acute hepatitis C, hepatitis C in injection drug users, complementary and alternative medicines and hepatitis C, and hepatitis C in prison parolees.
- $ The NIAID, in collaboration with the NIDDK and NIDA, has reissued a Request for Applications for Hepatitis C Cooperative Research Centers. These Centers promote multidisciplinary research and translation of basic research findings on the hepatitis C virus to practical problems. These Centers will be funded in fiscal year 2005.
- $ The NIAID also is conducting a phase 1 clinical trial using a prototype vaccine produced by private industry; renewing the Hepatitis Animal Model Network,

which will focus on the development of animal models to screen therapies and vaccines for hepatitis C and hepatitis B; and is supporting the HCV Sequence Database and developing an HCV Immunology Database to operate in conjunction with the HIV database.

Intersecting research and active collaborations in hepatitis C are found among many NIH components. The statutory Digestive Diseases Interagency Coordinating Committee (DDICC), which is chaired by the NIDDK, serves to coalesce and synergize the efforts of the many NIH Institutes and Centers that support hepatitis C research, as well as the efforts of other Federal agencies. The Committee strives to promote the exchange of information and the formation of collaborative relationships among its member organizations in order to combat the full range of digestive diseases, including liver diseases.

To further strengthen the commitment of the DDICC to liver disease research, a Liver Disease Subcommittee was formed in 2003. This Subcommittee is composed of representatives from NIH components with significant support of or interest in liver disease research. The Liver Disease Subcommittee is in the final stages of producing an *NIH Action Plan for Liver Disease Research*, under the direction of the new NIDDK Liver Disease Research Branch, and with significant contributions from the scientific and lay community. It identifies current challenges and future opportunities for NIH-supported research on several types of liver disease, including hepatitis C.

The new NIDDK Liver Disease Research Branch, of which I am the Director, was established in 2003 to promote research efforts in critical areas of liver disease, such as hepatitis C. A major charge of the Branch is to improve collaborations and promote liver disease research in other NIH Institutes and Centers.

OUTREACH AND PUBLIC EDUCATION EFFORTS

Information-dissemination and public and professional education activities supported by the NIH in hepatitis C benefit from the coordinating focus provided by the National Digestive Diseases Information Clearinghouse of the NIDDK, and include the involvement of multiple NIH Institutes, other Federal agencies, and professional and lay organizations such as

the American Association for the Study of Liver Diseases, the American Liver Foundation, and the Hepatitis Foundation International. Information and facts sheets on hepatitis C and its treatment and prevention are also provided to the public online through two NIH websites maintained by NIDDK and NIAID, accessible, respectively, at: http://digestive.niddk.nih.gov/ddiseases/topics/hepatitis.asp and http://www.niaid.nih.gov/publications/hepatitis.htm. NIH-supported informational materials available on these websites include publications geared towards the general public, such as "What I Need to Know About Hepatitis C," "Chronic Hepatitis C: Current Disease Management," and "Hepatitis C: Information Resources." The Veterans Health Administration and the Centers for Disease Control and Prevention maintain comprehensive hepatitis C websites with educational materials of relevance to veterans as well as the general public at: http://www.hepatitis.va.gov/, and http://www.cdc.gov/ncidod/diseases/hepatitis/c/index.htm.

NIH ACTION PLAN FOR LIVER DISEASE RESEARCH

As I alluded to previously, the NIH is now completing a new research planning process for liver diseases, including hepatitis C, under the auspices of the statutory Digestive Diseases Interagency Coordinating Committee. An *NIH Action Plan for Liver Disease Research*, produced in consultation with external scientific and lay experts, will be released very soon. We believe that this planning effort will help to guide future research directions.

This Action Plan is the result of consultation and advice from hundreds of researchers, physicians and laypersons concerned with liver disease research. It outlines research goals for the future, goals that are short-, intermediate-, and long-term and low-, intermediate-, and high-risk. Hepatitis C was, of course, an important component in this Action Plan. While the final draft of the Plan is still undergoing review and approval, let me summarize the Action Goals that were particularly applicable to hepatitis C.

First, in the area of diagnosis and evaluation of patients, a major goal is to develop better means of assessing hepatitis C clinically, to determine its severity, stage, and presence of possible complications. Is the disease mild or severe? Early or late? Is cirrhosis present? Is

liver cancer present? Currently, our tools are limited—we rely upon liver biopsy and expensive and elaborate x-rays to assess the liver. A goal for research is to develop simple and reliable markers for hepatitis disease activity and stage, biomarkers for the presence of fibrosis or cirrhosis of the liver, and importantly, noninvasive markers for the presence of liver cancer, so that it can be detected readily at an early stage, when it is small and possibly curable by surgery. Thus, development of biomarkers for hepatitis C is a high priority and is already the focus of several trans-NIH initiatives in research.

Second, in the area of therapy, the current standard regimen of peginterferon and ribavirin therapy is unsatisfactory in several respects. It yields cures of disease in only half of patients, is expensive, and often requires prolonged treatment. Also, peginterferon and ribavirin have many side effects, and therapy is often not tolerated or cannot be used at all because of other medical problems—kidney failure, heart or lung disease, severe anemia, immunodeficiency, or psychiatric illness. One of the major goals for research in hepatitis C is to increase the response rate to therapy. This will require new drugs with new targets for the disease. The targets for therapy of hepatitis C have been uncovered by basic research on this virus, and they include a protease and a polymerase, similar to those of HIV, the AIDS virus. Investigators from both the NIH and private industry are involved in developing better therapies for hepatitis C. There have been more than 50 patent applications filed for new therapies of hepatitis C. At least six drugs are currently in early human trials. None of these agents are ready for licensure or approval, but preliminary results are promising and make us believe that a therapy will be available within the next ten years that is beneficial in more than 90 percent of patients with this disease. Research on therapy is focusing on developing new tools as well—a tissue culture system and small animal models that could be used to screen new drugs and new approaches to treatment of this disease. Furthermore, clinical trials are under way to help refine current treatments of hepatitis C and new uses of the medications that we have, such as use of long-term peginterferon or long-term ribavirin to control (rather than cure) hepatitis C. These trials are funded in collaborative fashion by NIDDK, NIAID, NIDA, NIAAA, and NCI.

Third, in the area of prevention, a major goal for research in the next ten years is to develop a hepatitis C vaccine. Understanding of the immune response to hepatitis C, and the

mechanisms by which people recover from this infection, are areas of research that are directed at how the immune response can be manipulated to prevent infection or ensure recovery once infection has occurred. Hepatitis C vaccine development is a major area of research by the NIH. In early 2005, the NIAID, in collaboration with NIDDK, will be hosting a workshop on "Progress in Developing Hepatitis C Vaccine." It is important to point out that the difficulties we face in combating hepatitis C are similar in many respects to those faced in HIV infection. Thus, research and progress in developing an HIV vaccine are likely to impact on research on an HCV vaccine. Alternative approaches to vaccine formulation that work against HIV are likely to work against HCV and *vice versa*.

We believe that the *NIH Action Plan for Liver Disease Research* will produce useful guideposts for prioritization in NIH program development, and will help synergize cross-cutting research efforts across the NIH.

Mr. Chairman and Members of the Committee, I hope that these few examples convey the firm commitment of the NIH to combating hepatitis C. The central mission of the NIH is to conduct and support biomedical research aimed at decreasing the burden of disease in the United States. In hepatitis C, I believe that the NIH's mission is being well served and that the future is encouraging for the ultimate control, cure, and prevention of hepatitis C in the American population. Let me conclude with a note of special thanks to the members of the Congress of the United States on behalf of the community of scientists who work in hepatitis C. Thank you for the continuing support of biomedical research through which we hope to improve the health of Americans.

I appreciate the opportunity to address the Committee on behalf of the NIH and would be pleased to respond to any questions you may have.

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Dr. Hoofnagle received his undergraduate degree from the University of Virginia in 1965 and medical degree from Yale Medical School in 1970. He did an internal medicine internship and residency at the University of Virginia Hospital (1970-72) and further internal medicine training and a hepatology-gastroenterology fellowship at the Veterans Administration Hospital in Washington, DC (1975-78). He was a research associate with the Hepatitis Branch of the FDA from 1972 to 1975, where he first engaged in hepatitis research. In 1978, Dr. Hoofnagle joined the Liver Diseases Section of NIDDK as a senior investigator in the Clinical Center of the National Institutes of Health. Over the next several decades he conducted laboratory and clinical research on viral hepatitis B and C as well as autoimmune liver diseases such as primary biliary cirrhosis. Dr. Hoofnagle was the first to describe the effects of interferon alfa in hepatitis C and has conducted many of the pivotal trials of antiviral therapy in hepatitis B, C and D. From 1986-88, he served as the clinical director of NIDDK and from 1988 to 2004 as the Director of the Division of Digestive Diseases and Nutrition, NIDDK. In July 2004, Dr. Hoofnagle was appointed director of the newly formulated Liver Disease Research Branch of NIDDK. Dr. Hoofnagle is the author of over 200 research and review papers and has edited three books and several research conference proceedings. He is a former president of the American Association for the Study of Liver Diseases (AASLD). He is the recipient of many honors and awards, including the distinguished achievement award of the

AASLD and the prestigious Shelia Sherlock prize for his contributions to liver disease research.