HEPATITIS PANELS

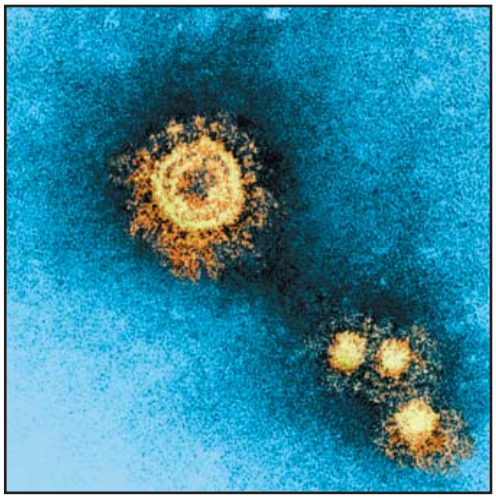
[Established 1979]

It has become customary in the U.S.–Japan Program to hold a special symposium before creating a new panel. The establishment of the Hepatitis Panels in 1979 was no exception; in July 1978, the USJCMSP held a symposium in Tokyo to discuss hepatitis research. The following year, at its 15th meeting, held at the NIH in Bethesda, Maryland, the Joint Committee approved guidelines for the new Hepatitis Panels. At the time, Dr. Norio Suwa had just replaced Dr. Toshio Kurokawa as Chair of the Japanese Delegation, and Dr. Ivan Bennett was Chair of the U.S. Delegation, a position he had held since the death of Colin MacLeod in 1972. Dr. Bennett was one of several scientists who strongly advocated the formation of the Joint Hepatitis Panels. The Joint Hepatitis Panels met for the first time in New York, from March 24–25, 1980.

Like other USJCMSP panels and boards, the Hepatitis Panels meet annually in a joint conference to review the field, raise awareness of important research directions to pursue and, particularly in Japan, communicate to Government funding officials the need for research support. In the United States, hepatitis research is funded through a variety of mechanisms and from several sources. The largest single source of funding is from competitive NIH grants, but the NIH also supports extensive hepatitis research in its intramural laboratories. Also, the private sector supports research in this area.

Viral hepatitis was—and is—a major health problem in the United Sates and Japan, as well as in other countries. The liver disease is caused by several viruses, known today as hepatitis A, B, C, D, and E viruses. Hepatitis B and C viruses cause the most serious disease; infection with either virus can progress from acute to chronic, and liver cancer can result.

In 1979, however, three kinds of hepatitis viruses were recognized: hepatitis A virus (HAV); hepatitis B virus (HBV); and a third type, then called non-A non-B but later named hepatitis C virus. [See text box.] At the time, HAV was the leading cause of acute hepatitis in the United States and a common cause of hepatitis in many Asian countries, and methods had been developed for its propagation in cell culture. When the Hepatitis Panels were established, HBV was well characterized, and intense efforts were underway in Japan, the United States, and Europe to develop an effective vaccine for preventing HBV.



Hepatitis B virus

An estimated 2 billion people worldwide have been infected with HBV, and more than 350 million are chronically infected. Young children who become infected with HBV are most likely to develop chronic disease, and an estimated 25 percent die from HBV-related cirrhosis of the liver or liver cancer. HBV infections are most prevalent in sub-Saharan Africa, Asia, and the Pacific. In 1982, a vaccine for HBV became available and, in 1991, the World Health Organization initiated a program for global vaccination against HBV.[1]

Today, hepatitis C virus (HCV) infects an estimated 3 to 4 million people annually, and causes chronic infection in an estimated 170 million people worldwide (3 percent of the world's population). Approximately 80 percent of newly infected individuals develop chronic infection, which then

causes liver cirrhosis in 10 to 20 percent of chronically infected people, and liver cancer in 1 to 5 percent. Disease prevalence is higher in certain African, Eastern Mediterranean, Southeast Asian, and Western Pacific countries than in North America and Europe. Despite intensive efforts, there is no vaccine to prevent HCV infection.[2]

Two of the most important contributions of the USJCMSP Hepatitis Panels were the discovery, in Japan, that HCV can cause liver cancer, and the development and testing of effective therapies for treating HCV infection. "The Japanese are very sensitive to hepatitis C infection and the resulting cancer," said Dr. Akira Oya in an August 2004 interview. Dr. Oya was a Member of the Japanese Delegation from 1989 to 2002, Member of the Japanese Panel on Viral Diseases from 1975 to 1989, and Chair of the Japanese Panel on Viral Diseases from 1985 to 1989. "But in the United States, they didn't realize that hepatitis C led to liver cancer," he continued. "Gradually, we made the case, and now the U.S. realizes that hepatitis C is an important cause of liver cancer." In Japan, he says, about 80 percent of liver cancer is caused by hepatitis C. The cancer typically develops 10 to 20 years after the infection.

Dr. Hiroo Imura, a member of the Japanese Delegation from 1991–2002, agrees. "Studies on hepatitis in Japan are made easier because, unfortunately, we have many patients with hepatitis infection," he said in an interview in August 2004. "Recently, we have seen many more infections with hepatitis C, probably because of the use of infected needles. We postulated that the hepatitis C virus was carcinogenic, but the United States did not believe us. At that time most people did not believe it."

Indeed, researchers and clinicians associated with the Japanese Hepatitis Panel found that many Japanese patients with hepatocellular carcinoma had circulating antibodies to HCV. Retrospective analyses indicated that until the late 1970s mortality due to HCV-caused liver cancer in Japan had been comparable to that of HBV-associated cancer. (The HBV/HCV ratio in hepatocellular carcinoma patients at that time was 50/50, and the ratio showed a linear increase to 80/20 at the end of the 20th century, probably due in part to the introduction of the HBV vaccine). In the mid-1990s, the U.S. Hepatitis Panel demonstrated a similar trend in the United States. Thus, HCV was recognized as an important cause of liver cancer, as had previously been demonstrated for HBV. USJCMSP scientists from Japan and the United States continued to study the association between HCV and liver cancer, and subsequently confirmed the carcinogenic effects of HCV protein expression in transgenic mice.

In a related development, even before HCV was discovered, clinicians associated with both the United States and Japanese Panels recognized the efficacy of using alpha-interferon to treat chronic HCV infection. Based largely on the results of a Japanese clinical study, interferon treatment is considered likely to prevent the development of cancer as well as reduce viral replication and hepatic inflammation, endpoints that have been observed in multiple clinical trials.

"Interferon is effective in treating in hepatitis C, but its efficacy varies with race and ethnicity," said Dr. John La Montagne in a September 2004 discussion. Dr. La Montagne was U.S. Program Director for the USJCMSP from 1988–2004. The problem was addressed in large, well-controlled, prospective, randomized clinical trials carried out by teams of investigators associated with the U.S. Hepatitis Panel. The results of these trials indicated the added benefit of therapeutic regimens that combine alpha-interferon with ribavirin, and the use of pegylated forms of interferon rather than conventional interferon formulations.

The following list includes other important science advances in hepatitis research to which USJCMSP scientists have contributed. Dr. Shunji Mishiro (Chair of the Japan Hepatitis Panel from 2000–present), Dr. Stanley M. Lemon (member of the U.S. Hepatitis Panel from 1991–1995, and Panel Chair from 1996–present), and Dr. Rajen Koshy (Program Officer for the U.S. Hepatitis Panel) provided the information.

Hepatitis Panels
[Established 1979]

[Science Advances: 1979 – 2000]

- Recognized the association of HCV infection with liver cancer and fulminating hepatitis. [See discussion above]
- Conducted clinical studies to determine the effectiveness of alpha-interferon and other antiviral drugs for treating chronic infections with hepatitis viruses. This has led to the licensing and use of alpha-interferon for HCV, the combined use of alpha-interferon and ribavirin (another antiviral drug), and to the development and licensure of other small-molecule, antiviral agents that inhibit the replication of hepatitis B and C viruses. [See discussion above]
- Helped stimulate research on HCV, including studies that led to the cloning of HCV. In 1979, some patients with apparently infectious liver diseases showed no evidence of either HAV or HBV infection, which, at the time, were the only known viral causes of hepatitis. The USJCMSP Hepatitis Panels recognized the need to identify the mysterious origin(s) of what was then known as non-A, non-B hepatitis. During the 1980s, scientists associated with both the U.S. and Japanese Hepatitis Panels began an intense effort to determine the possible existence of additional hepatitis virus(es). They demonstrated the existence of chloroform-sensitive and chloroform-resistant forms of non-A, non-B hepatitis by successful passage of the agents through chimpanzees. The animals developed hepatitis and their liver cells showed ultrastructural changes. Then, in 1989, researchers associated with the U.S. Hepatitis Panel discovered HCV by molecular cloning of the chloroform-sensitive non-A, non-B hepatitis agent, and published the nearly complete nucleotide sequence of the RNA genome of HCV. Soon after that, researchers associated with the Japanese Panel reported missing 5'-terminal nucleotide sequences. These discoveries led to the identification of the entire RNA sequence of the hepatitis C virus genome.
- Helped stimulate research on hepatitis E virus. As research on HCV was progressing, a different research team associated with the U.S. Hepatitis Panel cloned another non-A, non-B agent, and named it hepatitis E virus (HEV). HEV corresponded to the chloroform-resistant non-A, non-B agent, and was later demonstrated to be the cause of the "water-borne hepatitis" that is endemic in some tropical and subtropical developing countries in both the eastern and western hemispheres.
- Helped promote the development of vaccines against HBV, and initiated efforts toward universal immunization against HBV, a public health advance that has decreased rates of hepatocellular carcinoma related to HBV in populations at risk. In 1979, investigators associated with the U.S. Hepatitis Panel reported the results of a pivotal clinical study of a formalin-inactivated, plasma-derived HBV vaccine, demonstrating the safety and exceptionally high efficacy in the prevention of clinical and subclinical HBV infections among persons at high risk for the disease in New York City. A vaccine manufacturer in the United States subsequently developed a yeast-derived recombinant HBV vaccine that was shown to have a safety and efficacy profile equivalent to the plasma-derived vaccine. Such vaccines are now in widespread use throughout the world. They are produced in Japan and the United States, as well as other countries. HBV vaccines can prevent the long-term complications of HBV infection, including hepatocellular cancer.
- Developed vaccines containing inactivated HAV, which has provided effective, active prophylaxis against the predominant causative agent of endemic infectious hepatitis. In 1986, investigators associated with the U.S. Hepatitis Panel demonstrated that a formalin-inactivated HAV vaccine produced from virus propagated in cell culture was capable of preventing HAV infection in non-human primates. A formalin-inactivated HAV vaccine produced by an American vaccine manufacturer subsequently was demonstrated to be highly effective in prevention of endemic HAV among children in a randomized, prospective clinical trial. Such vaccines are now produced by manufacturers in many countries, including both the United States and Japan, and are widely used for preventing HAV infection.
- Molecular characterization of HCV. Following its discovery, intensive efforts by virologists associated with the Japanese and U.S. Hepatitis Panels led to the identification of at least 11 viral proteins that are expressed by HCV, including at least three enzymatic activities: a virally encoded RNA-dependent, RNA polymerase, a serine protease, and an NTPase/helicase. Additional studies by academic and industrial scientists in both countries have led to understanding the structure and function of many of these proteins. Investigators associated with the U.S. Hepatitis Panel contributed substantially to the development of the replication-competent subgenomic and genome-length HCV RNAs that are capable of autonomous replication in cultured cells, an advance that paved the way for more effective antiviral drug-discovery efforts.
- Eliminated the hepatitis B and C viruses from the blood supply, which had been the predominant causes of transfusion-associated hepatitis in Japan. As a result, there has been a dramatic decrease in transmission-associated HCV infections. After the discovery of HCV and the implementation of screening units of donor blood for antibodies against HCV, in addition to the pre-existing testing for HBV (carried out using different testing paradigms in both countries), the incidence of post-transfusion hepatitis decreased substantially in both the United States and Japan. Both countries subsequently introduced newer, high-sensitivity screening tests that are

based on detecting HBV and HCV nucleic acid. The tests, called nucleic acid testing (NAT) of donor blood units, have been introduced in Japan and have helped prevent additional cases of post-transfusion hepatitis.

[Recent Science Advances: 2000 – 2004]

- Ongoing research to promote the development of safer and more effective therapies for HCV infection, based on an improved knowledge of the molecular biology of the virus. By Fall 2004, clinical studies were underway with small molecule inhibitors of both the NS3/4A protease and the NS5B RNA-dependent RNA polymerase. Such efforts show strong promise of less expensive, safer, and more effective therapeutic regimens. Other recent studies from Japanese investigators suggest that the immunosuppressant cyclosporin A may have antiviral activity.
- Improved understanding of the molecular mechanisms by which HCV evades the immune system. Studies with HCV RNA "replicons" carried out by scientists associated with the U.S. Panel have shed new light on the mechanisms of the HCV immune evasion that contributes to the persistence of this virus in infected humans, including mechanisms for evading induction of interferon.
- Provided epidemiological evidence that humans who clear one HCV infection have long-lived immunity against a second infection. When combined with similar results from animal models, the new results, obtained by USJCMSP scientists associated with the Hepatitis Panels, suggest it may be possible to vaccinate against persistent HCV infection.

Footnotes — Hepatitis Panels

[1] World Health Organization. Hepatitis B Fact Sheet No. 204. http://www.who.int/mediacentre/factsheets/fs204/en/.

[2] World Health Organization. Hepatitis C Fact Sheet No. 164. http://www.who.int/mediacentre/factsheets/fs164/en/