Japanese Study of Liver Diseases from an International Perspective
—History of the past 50 years and future prospects—


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Abstract
Recollecting the author’s personal experience, this article reviews the past 50 years in which the study of liver diseases in Japan developed through interaction with hepatologists in the world. The Japanese academic society dealing with liver diseases was founded in 1959 as the Japanese branch of the International Association for the Study of the Liver (IASL). It evolved into the Japan Society of Hepatology 5 years later, and the Society celebrated its 42nd anniversary last year. In this period, Japan hosted two IASL meetings, as well as various international symposia. Activities across national borders have also been increasing. The number of presentations from Japan accepted by the American Association for the Study of the Liver Diseases (AASLD) is now only second to that from the U.S. An important contribution Japan can make to the world may be the sharing of its ample clinical experience and study results concerning hepatocellular carcinoma.

Key words IASL, APASL, AASLD, Japan Society of Hepatology, Hepatocellular carcinoma

Introduction
It was 1957 when I graduated from medical school. Starting from that time, I wanted to retrace how the study of liver diseases in Japan has developed over the past 50 years and how it has been positioned from an international perspective, referring to my own experience and suggesting future directions.

Establishment of the International Association for the Study of the Liver (IASL) and the Japanese Branch of the IASL

In May 1958, the year after graduating from medical school, the first World Congress of Gastroenterology was held in Washington D.C., U.S. On this occasion, the people who envisioned a study organization of hepatologists all over the world held a preparatory meeting for the establishment of the IASL. Professor Sadataka Tasaka (University of Tokyo) (affiliation and position are those at that time, as with the following) and Professor Tsuneo Yoshida (Osaka University) attended this meeting from Japan and were asked to set up the Japanese branch. This was probably the first interaction between hepatologists in Japan and other countries after World War II.

In the U.S., the first meeting of the American Association for the Study of Liver Diseases (AASLD) was organized by Professor Popper (Mount Sinai Hospital) as early as in 1959. In the same year, the general meeting of the IASL Japanese branch was held in Matsumoto City under the lead of President Sadataka Tasaka. The quick response of Japan in establishing this organization immediately after its American counterpart

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signified that the study of liver diseases in Japan had progressed to a considerable level. In fact, this progress was convincingly reflected in the quality of presentations given at the meeting.

In the following year, 1960, the first IASL meeting was held in London under Professor Sherlock (Royal Free Hospital), the first president. While the World Gastroenterology Organization (WGO) and the IASL were created almost at the same time as places for international exchange, the IASL started as a closed circle of limited members. The WGO was therefore important as an open place for study presentation.

I first attended an international meeting in 1961, when Professor Popper visited Japan for the first time and a study discussion meeting was held at Gakushikaikan Akamon Hall of the University of Tokyo. As a postgraduate student, I presented my work on the electron microscopic study of intrahepatic cholestasis and was praised by Professor Popper. As a development from this occasion, my mentor Professor Seizo Miwa (Chiba University) served as a panelist in the symposium on intrahepatic cholestasis chaired by Professor Popper during the second World Congress of Gastroenterology in 1962 in Munich, Germany. I also spoke in the general academic program. At that time, the overseas travel of Japanese people was restricted under a national policy.

The second IASL meeting was held immediately after the World Congress of Gastroenterology in Germany. The third World Congress of Gastroenterology was then held in Tokyo in 1966, followed by the third IASL meeting in Tokyo and Kyoto under the lead of Professors Tadao Takahashi (Jikei University) and Masanori Masuda (Kyoto Prefectural University of Medicine) chairing the organizing committee. With as many as 14 Japanese speakers presenting their work, this meeting proved a good opportunity to introduce Japanese hepatology to the world. I spoke on the role of hepatic lymph in the development of ascites and jaundice, and received great commendation from Professor Sherlock, who chaired the session.

The IASL meeting was held at 4-year intervals and then at 2-year intervals at various venues in the world. The number of members increased, and the process for submitting a report became less difficult. Professor Kunio Okuda (Chiba University) served as the president for some time in this period. I chaired the organizing committee for the 2000 IASL meeting in Fukuoka.

As mentioned above, the IASL and the WGO were important for a long time as top-level international academic societies and as places for international exchange in the study of the liver. However, both organizations have recently been shifting their emphasis from the exchange of high-level research information to the popularization of knowledge and therapeutic technologies regarding gastrointestinal and liver diseases.

The Asian Pacific Association for the Study of the Liver (APASL) has been promoting the study of the liver and mutual interaction of researchers in Asian regions. The first meeting was held in 1980 under the presidency of Professor Powell (University of Queensland). Later meetings were held at 2-year intervals, and the meeting in 2000 was held jointly with the IASL meeting in Fukuoka under the presidency of Dr. Michitami Yano (Director, Nagasaki Medical Center). The next meeting is planned to take place in March 2007 in Kyoto under the presidency of Professor Masao Omata (University of Tokyo). I am glad to see the steady growth of the APASL, helping the enhancement of the study of liver diseases in Asian countries. Japan is expected to be a good leader in this organization.

The Role of the Japan Society of Hepatology

The organization created as the Japanese branch of the IASL changed its name to the Japan Society of Hepatology in 1965. The first general meeting of the Society was held this year under the presidency of Professor Tadao Takahashi (Jikei University), and the 42nd general meeting was held in May 2006 under the presidency of Professor Takeshi Okanoue (Kyoto Prefectural University of Medicine).

Considering the high level of hepatology in Japan, I believed that the study of liver diseases in the world should be promoted through friendly rivalry among the AASLD, the European Association for the Study of the Liver (EASL), and the Japan Society of Hepatology. When I was the president, I wanted to organize the 31st general meeting as a full-fledged international meeting. English was used as the official language, and symposia and general presentations were chaired by foreign and Japanese researchers in equal numbers. The purpose was to internationalize the
already high-level society in Japan on the one hand, and to let the people in the world know the level of hepatology in Japan on the other. The meeting was successful with about 150 participants from overseas. However, it is regrettable that none of later presidents followed this approach.

During my term as the director general of the Japan Society of Hepatology (form April 1996 to June 2000), the society decided to promote international contribution as a major objective and launched the International Symposium on Liver Cirrhosis and Liver Cancer. With particular emphasis on interaction with people in Asian countries, the symposium was held four times starting from 1996. After Professor Kiwamu Okita (Yamaguchi University) became the director general, a single-topic conference was held every year inviting top-class researchers from the world. This event has continued successfully to the present day.

As outlined above, the Japan Society of Hepatology is working with strong interest in international contribution.

The AASLD and Other Developments

As mentioned above, the position of the WGO and the IASL as the center of international exchange and places for high-level academic discussion has been taken over by the AASLD. One of the factors causing this change was the high level of basic study in the U.S. The recent discovery of the hepatitis virus causing liver disease and the development of anti-hepatitis virus agents both took place in the U.S. It was not surprising that the association in the U.S. became the center of information exchange regarding the study of liver diseases. Japan, as well as European countries, definitely has a insufficient number of researchers in virology in comparison with the U.S.

Recently, the number of presentations from Japan at the AASLD meeting has been increasing steadily. The number of presentations accepted at the 2005 meeting in San Francisco, summarized by country, is as shown in Table 1. While the U.S. was in the first place with 486 presentations, Japan was in the second place with 176 presentations, running ahead of Germany and the U.K. by a large margin. This number alone indicates the activity of study in Japan. While the AASLD is now the center of international exchange in the study of the liver, the EASL is also making remarkable progress in enhancing the level of study.

Aside from the main activities of the society in the field of liver diseases, Japanese researchers have also been active in international conferences, study meetings, and symposia related to the liver. Under the framework of the US-Japan Cooperative Medical Science Program based on the agreement made in 1965 between U.S. President Johnson and Japanese Prime Minister Sato, the working team on hepatitis has been holding joint study meetings, starting from the first meeting in 1980 in New York. The chief of the working team on the Japanese side was Professor Toshitsugu Oda (University of Tokyo) at the beginning and is Dr. Shunji Mishiro (Toshiba General Hospital) at present. The joint meeting has been held alternately in Japan and in the U.S. I worked for the one held at Huis Ten Bosch in Nagasaki with great success.

A memorable event in this respect was the International Symposium on Viral Hepatitis and Liver Disease, which was held in Tokyo for 5 days in 1993 under the presidency of Dr. Kusuya Nishioka (Viral Hepatitis Research Foundation of Japan). The symposium was successful with many attendants from overseas. It also demonstrated the strength of the study of the liver in Japan. On the other hand, Professor Hiromasa Ishii (Keio University), who was at the center of the study of alcoholic liver disease in Japan, organized the meeting of the International Society for Biomedical Research on Alcoholism (ISBRA) in Yokohama in 2000. This event was also a great success. Professor Isao Okazaki (Tokai Univer-

| Table 1 Number of presentations at the AASLD meeting by country, top 10 countries |
|--------------------------------|---------|
| 1 USA                         | 486     |
| 2 Japan                       | 176     |
| 3 Germany                     | 114     |
| 4 UK                          | 106     |
| 5 France                      | 99      |
| 6 Italy                       | 65      |
| 7 Spain                       | 46      |
| 8 Canada                      | 41      |
| 9 Australia                   | 37      |
| 10 Netherlands                | 35      |

(Total number of presentations: 1,393)

Starting from when I was on the postgraduate course, I have been enthusiastic about the electron microscopic study of liver tissues. At that time, Igaku-Shoin Ltd. was eagerly looking for opportunities to publish medical books written in English, and the company proposed to publish my book on the electron microscopy of the liver. This offer resulted in “Ultrastructural Aspects of the Liver and its Disorders,” a book of 237 pages published in 1968. As there were no other books of this kind in the world, my book was accepted as a textbook for researchers in this field. It was distributed by Springer in Germany, and Spanish and Italian translations were produced by publishers in respective countries. I am confident that this book, sold all over the world, greatly helped the reputation of Japanese study of liver diseases. I was 35 years old at that time. More recently, many monographs in the field of liver diseases written by Japanese authors have been published, such as those of Professor Kunio Okuda.

In addition, Japanese researchers were particularly enthusiastic about the study of sinusoid cells. The Japanese forerunner in this field was Professor Toshio Itoh (Gunma University), who discovered Itoh cells, now generally known as hepatic stellate cells. I also was interested in these cells and conducted several studies on them. The term “sinusoid cells” generally refers to Kupffer cells, sinusoid endothelial cells, hepatic stellate cells, and Pit cells (NK cells). An international study association on these cells was organized by Professor Wisse (University of Leiden), who was in the Netherlands at that time. I was invited to the first symposium in 1977 and spoke on the clinical relevance of these cells. This symposium has been held at 2-year intervals. The one in 1994 was held in Kyoto under the lead of Professor Kenjiro Wake (Tokyo Medical and Dental University), and was a great success. As I was much interested in these cells after attending the first symposium, as well as because of the importance of these cells, I set up a study group on sinusoid cells in Japan. This year, the study group celebrates its 20th anniversary. The study of sinusoid cells in Japan is the most active and most advanced in the world.

**Future Directions**

The study of liver diseases in Japan is at the top level in the world, only second to that in the U.S. This fact is testified by the number of presentations at the AASLD meeting and the number of papers in various journals. Membership of the Japan Society of Hepatology has exceeded 10,000 persons. No other academic society in the field of liver study has this many members. However, it seems that Japan is not showing sufficient leadership in the study of liver diseases in the world. The largest problem is the relative scarcity of unique studies originating in Japan despite the abundance in number.

One of the reasons is the fact that a great many young Japanese researchers have studied in the U.S. in the past 30 years, continuing to study in the American way after returning to Japan. I do not understand why so many people want to study in the U.S. now, decades after the post-war era, but I suspect that studying abroad has been a factor inhibiting unique studies in Japan. During my 21 years of tenure as a professor, I did not allow my students to study abroad as a rule. It was because I believed in the value of thinking by oneself and conducting study by oneself. Speaking of the uniqueness of study, I remember Dr. Toshio Shikata, Professor Emeritus of Nihon University, who invented the staining of HBs antigen-positive cells known as Shikata’s stain, and Dr. Kazuo Okouchi, Professor Emeritus of Kyushu University, who discovered the relationship between the Australia antigen and hepatitis B virus.

The second reason is the fact that there are few persons with a good command of English, in particular among those in leading positions. Furthermore, Japanese people are not good at discussion. Japanese researchers must try to be more active in discussions at international academic meetings. Poster sessions are no exception. It is a starting point for global partnership.

The largest clinical theme in front of us at present is liver diseases related to hepatitis virus. Achievements in this field, from basic study to the development of antiviral drugs, have mostly been made in the U.S. In this field, Japan is no match for the U.S. at present.

Then, what about the future? In my opinion, the coming years seem to provide a chance for
Japan to become the top leader in the study of the liver in the world, as it has been the top runner in the study of liver diseases.

First, I think so because of the study and treatment of hepatocellular carcinoma. This disease has been increasing rapidly in Japan for 30 years, 10 or 20 years before the beginning of the increase in the U.S. As a result, we have much more experience in hepatocellular carcinoma than European and American researchers. While the increase in hepatocellular carcinoma has recently been attracting attention in Western countries, Japan is ahead of them in basic and clinical study related to this disease. So, we have the opportunity.

Second, Western countries are now experiencing a remarkable increase in non-alcoholic steatohepatitis (NASH) resulting from obesity. This condition is emerging as an important theme in addition to the aforementioned hepatocellular carcinoma. NASH is also attracting much attention recently in Japan, and there is a growing recognition that this condition is not rare in Japan, either. Considering the genetic background of the Japanese people, I think that the prevalence of fatty liver or NASH in Japan is going to exceed that in the U.S. in a similar manner to type 2 diabetes mellitus. This type of fatty liver or NASH is currently considered as the liver manifestation of metabolic syndrome. However, I suspect that the changes in the liver may be the beginning of metabolic syndrome, because the liver is the center of various metabolic processes. I hope that Japan may take leadership in the study of liver diseases in the world through the promotion of the study of fatty liver and NASH and, furthermore, the study of metabolic syndrome focusing on the liver, in addition to the clinical and basic study of hepatocellular carcinoma.