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CONTENTS

- Changes in common knowledge about hepatitis B
- Position Paper: Considering proper provisions of In-vitro diagnostics
- Patient's Voice: Deepening the understanding of dystonia and its symptoms
- Voice from the Local Government: Aim to develop the "largest medical industry cluster" that contributes to the world
- The 6th AMDD Annual General Meeting
- AMDD participated in the Summer Vacation Event "Children's Day" in Kasumigaseki
- Value of Medical Technology -- Diagnostic and therapeutic devices
- AMDD media events - "Hepatitis B virus infection" and "safety of medical practitioners" -

Changes in common knowledge about hepatitis B

Hepatitis B virus (HBV), which causes hepatitis B, was discovered as the 'Australia antigen' in 1965. It now faces a new turning point since the conventional "common knowledge" no longer applies.

Sharp reduction of Japanese-type hepatitis B with selective vaccines

There are various genotypes (types of genes) of hepatitis B viruses (HBV) depending on race and region. Genotypes B and C are common in Japan, while Genotypes A and D are common in the United States and Europe. There are two major routes of transmission: vertical transmission and horizontal transmission. Vertical transmission refers to mother-to-child transmission in which viruses are transmitted from mothers to infants. Babies who are born to HBe antigen-positive HBV carrier mothers have a 90% or higher probability of carrying HBV. Horizontal transmission refers to transmission through sexual contact or blood.

In Japan, an HB vaccination program for newborns was initiated in 1986 across the country because reducing mother-to-child transmission was considered to be an effective approach to eradicating hepatitis B. This program employed selective vaccination, which administers HB vaccines only to babies born to HBs antigen-positive mothers. According to a survey in 2000, the percentage of HB carriers among people younger than 28 years old sharply decreased to 0.63%, giving Japan one of the lowest numbers of HBV-infected citizens in the world.

However, acute hepatitis of Genotype A, which had been very uncommon in Japan, has recently been increasing rapidly and now accounts for about half of patients. Most of these cases are horizontal transmission through sexual contact. Conventionally, it was

considered that acute hepatitis of Genotype B or C is completely curable and not chronic once treated if the virus is acquired in adulthood. On the other hand, acute hepatitis of Genotype A becomes chronic in about 10% of patients.

Reactivation of HBV by chemotherapy

Another problem is the reactivation of HBV by drugs that suppress the immune system. Traditionally, HBV infection was considered completely cured in HBs antigen-negative and HBs antibody-positive patients, although HBV carriers with stable hepatic function may show elevated hepatic function after immunosuppressant therapy, resulting in the development of fulminant hepatitis in rare cases. However, it has recently been found that even in these patients, administering certain immunosuppressants may reactivate HBV, potentially causing hepatitis or fulminant hepatitis. Even if the disease appears to be completely cured, HBV remains latent in the body and may undergo reactivation when triggered by immunosuppressants or other factors. Furthermore, HBs antibody-positive blood donors may spontaneously become HBs antigen positive without the use of the above-mentioned drugs, although the frequency is as low as about 1%, according to a Japanese Red Cross Society survey.

This means that our “common knowledge” has dramatically changed from “HBV disappears” after curing hepatitis to “HBV persists for life once infected” in HBs antigen-negative and HBs antibody-positive patients.

Since subsequent studies have shown that hepatitis and fulminant hepatitis can be prevented by measuring HBV-DNA at a certain interval during chemotherapy and administering antiviral agents immediately if HBV-DNA positivity is detected, a method of prevention has almost been established. However, the cost of this approach is enormous. Therefore, it is now necessary to establish an efficient preventive method based on cost effectiveness through the analysis of reactivation data from various diseases. The circumstances surrounding hepatitis B are entering a new phase.

*The lecture provided by Dr. Mizokami was summarized by the editorial desk.



Dr. Masashi Mizokami

Director General,

The Research Center for Hepatitis and Immunology,
National Center for Global Health and Medicine

Dr. Mizokami graduated from Nagoya City University Medical School in 1976 and studied abroad at King's College Hospital in England in 1989. He took up the post of Professor in clinical laboratory medicine at Nagoya City University Medical School in 2000, became Professor in the Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences in 2001, and then Director General of the Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine in 2008. He also serves as a member of the Council for the Promotion of Hepatitis Measures in the Ministry of Health, Labour and Welfare.

Position Paper

Considering proper provisions of In-vitro diagnostics

In line with the progress of scientific technology, clinical tests have been increasingly used for companion diagnosis or disease risk prediction as well as conventional disease diagnosis or follow-up, leading to the increased significance of these tests. In addition, providing POCT* and over-the-counter (OTC) test agents may support home care or nursing care and is expected to contribute to disease prevention and health maintenance of citizens, resulting in significant changes in the expected role of tests. In these situations, we should play an important role in properly providing in-vitro diagnostics to medical institutions, and examination or checkup sites. However, there are still many issues in Japan. For instance, some of the tests that have a large impact on individuals (for example, prenatal diagnosis and breast cancer risk test) are provided to citizens without governmental authorization or adequate guarantee of quality, performance, or accuracy. For the purpose of establishing a framework to provide clinical tests to citizens properly and as early as possible, the American Medical Devices and Diagnostics Manufacturers' Association (AMDD) recently issued its second Position Paper jointly with the Japan Association of Clinical Reagents Industries (JACRI) and in-vitro diagnostics committee of the European Business Council (EBC). This Position Paper offers the following three proposals, focusing on how to provide clinical tests properly and what role in-vitro diagnostics should play where the needs for clinical tests are increasingly diversified in response to the progress healthcare reform.

*POCT (point of care testing): Defined as clinical tests that are offered near the site of patient care, such as at the bedside, to provide prompt results.

Proposal 1: Appropriate category of clinical reagents and clarification of regulatory requirements in each category by taking advancement of testing technologies and diversification of clinical needs into account.

Currently, clarification of the clinical value in addition to the analytical validity of diagnostics is necessary to obtain the pharmaceutical approval of in-vitro diagnostics. As testing technology has become more sophisticated and complex and the purposes of clinical use have diversified, there are concerns that the period and scale of clinical trials are likely to be longer and larger, and the emergence of multiplex testing (for example, sequencing-based genomic tests) that can analyze multiple items simultaneously requires disease-based databases or analytical algorithms to demonstrate the clinical value, making it very difficult to demonstrate the clinical value of diagnostics. In order to provide diagnostics based on state-of-the-art technologies to clinical sites promptly and properly, the Position Paper reclassifies clinical test agents into appropriate groups (see the table below) and clarifies regulatory or operational requirements for each class to propose stepwise introduction to clinical sites.

Categories	Main requirements for regulatory review	Insurance coverage request by company
In-vitro diagnostics (IVDs)	Proof of analytic validity and clinical utility	Possible
Investigational Use Only (IUO)	Proof of analytic validity	Not possible
Other than IVDs and IUO	Not subject to marketing authorization review Use possible only for research purposes	Not possible

Proposal 2: Establishment of a system relating to clinical research with the aim toward the promotion and acceleration of IVD development.

In order to provide in-vitro diagnostics to medical sites as soon as possible, it is important to shorten the period required for development and review. Various improvement strategies have been undertaken for the review period, including the formulation of the first “Collaboration Plans to Accelerate Review (Fiscal 2014 to 2018)” for in-vitro diagnostics. Meanwhile, since ethical guidelines for clinical research have been tightened, long periods and high costs are required for diagnostic developers to conduct clinical performance tests, resulting in a prolonged period of development for in-vitro diagnostics and sometimes imposing a barrier to the development itself. The Position Paper makes the following two proposals so that clinical performance tests, which are the cause of the developmental barrier, can be conducted properly and promptly:

- (1) Formulate guidelines for clinical performance tests on the basis of the characteristics of in-vitro diagnostics
- (2) Create specimen banks that can be used in the development of in-vitro diagnostics and to establish rules for utilization

Proposal 3: Promotion of use of IVDs in home healthcare, nursing care, community healthcare, and self-care.

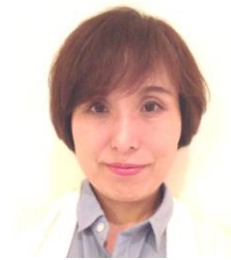
As the government tries to promote the community care system, improve home care and home nursing, enhance health maintenance of citizens, and promote disease prevention and early detection, it is considered possible to contribute to the improvement of home care and nursing care by providing and using POCT and OTC test agents properly as in-vitro diagnostics. However, assuring testing quality is another important challenge especially because of the simplicity of the tests. For the safe and proper management and popularization, it is necessary to improve both the hardware such as test agents and devices with greater precision control and ease of maintenance, and the software such as routine precision control and maintenance of devices as well as improvement of expertise and skills in their use or result interpretation. The Position Paper proposes the proper establishment of accurate and precise testing frameworks first, and then adequate insurance reimbursement to maintain such frameworks. These are so that POCT and OTC test

agents, which can be provided not only to medical institutions but also to various healthcare services, will be used to the maximum.

Conclusion

In response to the diversified needs for clinical tests, we will continue to make sincere efforts to clarify how in-vitro diagnostics used for testing should be provided properly.

(See http://amdd.jp/en/pdf/technology/en_pp_20140730.pdf for the Position Paper)



Ms. Miwa Nishida
Manager of the Regulatory & Clinical Development,
Operations, Logistics, Quality & Regulatory,
Roche Diagnostics K.K.

Patient's Voice

Deepening the understanding of dystonia and its symptoms



Mr. Shuichi Kawashima, Vice Director
Incorporated Non-profit Organization Dystonian Friends
Association

The Dystonian Friends Association, which was founded in 2005, has been seeking to improve the recognition of dystonia, which is an intractable neurological disease, by issuing newsletters and holding patient meetings or lectures. Dystonia is a disease in which some disorder in the brain (basal ganglia) disturbs the central nervous system, triggering involuntary contraction of particular muscles and resulting in limitations to free movement. The disease mainly develops in the eyelids (blepharospasm), neck (spasmodic torticollis), and hands (writer's cramp), and sometimes in the throat (spasmodic dysphonia), mouth and jaw, and feet. It may even extend to multiple sites or the whole body including the trunk, causing severe discomfort and disability in life if it worsens. The number of patients in Japan is estimated to be several tens of thousands, although actual data is unavailable. In addition to primary dystonia, there are also many patients with secondary dystonia caused by the effect of underlying diseases in the brain (cerebrovascular disorder, cerebral palsy, etc.) or adverse drug reactions of antipsychotics.

Only medication, botulinum treatment, surgical therapy, and acupuncture are currently available for dystonia. Botulinum treatment blocks abnormal neurotransmission at the

terminus by injecting a diluted solution of the toxin produced by Clostridium botulinum, which is known to cause food poisoning and is used in chemical weapons, to involuntarily moving muscles. Although it is only palliative, its application to the eyes and neck was approved in 1998 and 2001, respectively, and many patients are enjoying its benefits.

The mainstream of surgical therapy is a technology called deep brain stimulation (DBS). This method stimulates the target site with electric pulses to relieve the symptoms by placing electrodes in the target point of the brain and implanting a battery in the chest or abdomen by anesthetic surgery. It is sometimes referred to as a pacemaker of the brain and shows about 70% improvement on average, although the effect is different for each patient. If successful, even patients with generalized dystonia can regain free body movement to a level comparable to that of healthy people. It is especially wonderful that patients with severe symptoms who developed the disease in childhood have a chance to find new hope in life with DBS.

The Dystonian Friends Association contributed to insurance coverage of the latest DBS device for dystonia in cooperation with specialists. We also assisted in the production of a documentary film called “Dystonia” by a movie director and held film screenings in various locations. Actual scenes of DBS surgery were also included in the film.

The prompt application of these latest medical technologies is vital for patients with intractable diseases like us. While seeking the public’s understanding of this issue, we feel the necessity to make every effort we can as a patient group.

Incorporated Non-profit Organization Dystonian Friends Association
<http://www.geocities.jp/dystonia2005/index.html>

Voice from the Local Government

Aim to develop the “largest medical industry cluster” that contributes to the world



Mr. Masahiro Okoshi
Director of Medical Industry Cluster Promotion Unit, Fukushima Prefecture

Fukushima Prefecture set the development of “medical industry clusters” as one of the key initiatives of the reconstruction plan to generate new industries that would lead into new era after the Great East Japan Earthquake.

To achieve this goal, we are currently trying to support research and development, assist entry from other business areas, cultivate human resources, expand the market, and establish hubs.



To support research and development, we allocated roughly 14.2 billion yen for 53 projects providing two types of subsidies including the “Fukushima Medical and Welfare Devices Development Project Subsidy” to assist in the commercialization of medical devices and sophistication of company technologies. In this fiscal year, we also launched the “Fukushima Medical and Welfare Devices Development and Industrialization Project Subsidy” that subsidizes the improvement of facilities to assist in the industrialization of developed products, and allocated roughly 1.8 billion yen for seven projects.

Consequently, development and commercialization based on the excellent technologies of companies in Fukushima are advancing in various areas, such as development of a triage education and training system using tablet terminals in the field of disaster medical care and the manufacturing of a medical device that can easily and rapidly diagnose dry eye.

To expand the market, we are holding “Medical Creation Fukushima,” which is an exhibition for the design and manufacture of medical devices, which the AMDD also joined. In the last fiscal year, 211 companies or groups joined the exhibition, a new record. In addition, we will celebrate the 10th anniversary of the exhibition this fiscal year and also plan to hold a joint exhibition with the Japan Surgical Association.

To expand the overseas market, we joined the world’s largest medical device exhibition “MEDICA/COMPAMED” and concluded a memorandum for business-to-business exchange with Land Nordrhein-Westfalen, Germany on September 1. This partnership was in response to the adoption of the “Regional Industry Tie-up (RIT) Program” by the Japan External Trade Organization (JETRO).

To establish hubs, we are proceeding with the establishment of the “Fukushima Medical Device Development and Safety Evaluation Center (tentative name)” to provide integrated support from development to industrialization including the first safety evaluation of medical devices using large animals in Japan, with an aim to open the center in fiscal 2016.

Fukushima is one of the leading medical device-manufacturing prefectures in Japan, currently ranked fourth in terms of manufacturing volume of medical devices (108.9 billion yen [Annual Report on Statistics of Production by Pharmaceutical Industry in 2012]) and first in terms of manufacturing volume of machine and instrument parts for medical care (13.3 billion yen [Census of Manufacturers in Fiscal 2012]). Through these efforts, we hope to achieve 175 billion yen in manufacturing volume of medical devices in fiscal 2020, which is the end phase of the secondary reconstruction plan.

We will continue to develop the medical device industry clusters by supporting various industrial initiatives. We would like to ask for your continued support and consideration.

The 6th AMDD Annual General Meeting

The American Medical Devices and Diagnostics Manufacturers’ Association (AMDD) held its 6th annual general meeting on September 11, 2014. In the opening speech, Chairman Takashi Shimada (President, Medtronic Japan Co., Ltd.) looked back on a fruitful year where the “Pharmaceutical and Medical Device Law” was enacted in November 2013 and

will be enforced beginning November this year. He also announced for a successful upcoming year he hopes to further cooperation with concerned parties and increase the presence of the AMDD.

After the chairperson of each committee reported their activities, Dr. Nobuya Koyama, specially appointed professor and professor emeritus in medical policy and external affairs in the Faculty of Medicine, Toho University, gave a special lecture entitled “Medical Fee Revision (2014) Orientation of Medicine in the Future”. In this lecture he spoke from the perspective of “specializing/strengthening the function of medical institutions, their cooperation, and improving home care,” which is one of the key issues of reform this fiscal year. He talked about future challenges of reshaping the healthcare system by 2025 on the basis of his broad experience in clinical practice and as a member of the Central Social Insurance Medical Council.



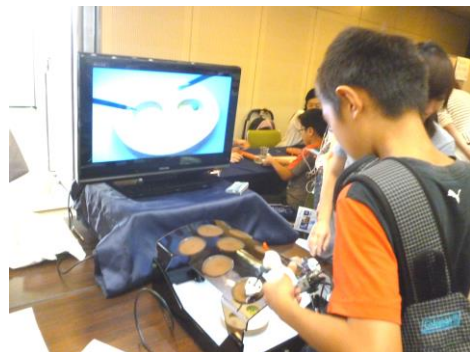
Takashi Shimada, Chairman of AMDD



Dr. Nobuya Koyama

AMDD participated in the Summer Vacation Event “Children’s Day” in Kasumigaseki

The American Medical Devices and Diagnostics Manufacturers’ Association (AMDD) joined “Children’s Day” in Kasumigaseki on August 6 and 7. This event jointly held by ministries and agencies every August promotes children’s understanding of society through visits to ministries and agencies in Kasumigaseki, and related work experience. The AMDD ran a booth in the ‘Devices and Machines to Find and Cure Diseases’ section in the Ministry of Health, Labour and Welfare. In this section, a total of 13 booths were set up by AMDD members and other companies so that children could touch and see medical devices. Much attention was drawn to devices and machines that they do not usually see, such as a device to suction thrombi and technology to immobilize bones, and this year again, many children visited the experience booths.



Value of Medical Technology <Diagnostic and Treatment Devices>

Intraoperative neuromonitoring

In surgeries inside the cranium or in the head and neck area, there is a risk of damaging cerebral nerves during the removal of a lesion. For example, if facial nerves are damaged, the muscles for facial expression are unable to move, resulting in a significant reduction in the quality of life (QOL) of patients. Therefore, not only is the goal the removal of the lesion but also the surgeries need to be careful to maintain neural function.

Intraoperative neuromonitoring is a device used to reduce nerve damage risk and has become increasingly popular in response to the need for improving the QOL of patients. On the other hand, there are problems such as the increased burdens of neuromonitoring procedures on healthcare professionals and increased costs.

Recently, a device that facilitates intraoperative neuromonitoring procedures was developed in response to these medical needs, and the insurance coverage for the additional expenses of surgical medical devices for neuromonitoring is expanding to reduce the financial



burden of hospitals. In surgeries of the thyroid or parathyroid gland, there is a risk of damaging the recurrent laryngeal nerve that controls the motion of the vocal cord, but the insurance reform of fiscal 2014 now covers additional expenses of surgical medical devices for intraoperative neuromonitoring in surgeries of thyroid or parathyroid malignancies. In the future, neuromonitoring is expected to become more popular and provide patients with safer and more effective medical care.

(Satoshi Murata, Medtronic Japan Co., Ltd.)

AMDD media events

- “Hepatitis B virus infection” and “safety of medical practitioners” -

The American Medical Devices and Diagnostics Manufacturers’ Association (AMDD) held a joint media seminar with the Japan Association of Clinical Reagents Industries (JACRI) on May 22 and the 24th AMDD media lecture on August 28.

In the third JACRI/AMDD joint media seminar, Dr. Masashi Mizokami, Director General of the Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, offered a lecture entitled “Current Situation and Issues of Hepatitis B Virus Infection in Japan,” which is about the change in common knowledge about hepatitis B (see the article on page 1 for a summary of his lecture).

In the 24th AMDD solo media lecture, the Safe Handling of Hazardous Drugs was chosen as the theme of the first program in the Safety of Medical Practitioners series. Dr. Johan Vandenbroucke, Hospital Pharmacist of the University Hospital Gent - Central Pharmacy and Former President of the International Society of Oncology Pharmacy Practitioners,

gave a lecture from a global perspective about the risk of “hazardous drugs” that may jeopardize medical practitioners, and assuring safety against this risk; and Dr. Shigeki Kohda, Senior Researcher of the National Institute of Occupational Safety and Health, Japan, gave a lecture about the current situation and issues in Japan for handling hazardous drugs (summaries for these lectures will be featured in the next issue).

This lecture series will be offered in three programs to promote a broader understanding of risks that medical practitioners are exposed to during medical practice and possible actions to be taken.



Left: Dr. Johan Vandenbroucke Right: Dr. Shigeki Kohda
Product exhibition related to the safety of medical practitioners in the 24th media lecture

Value of Medical Technology

Our mission is to make more people understand the unlimited potential of advanced medical technology and its contribution to the reformation of the Japanese medical care system

Note: All opinions in this newsletter are the personal opinions of the authors, and do not necessarily represent the opinions and activities of AMDD.