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A Global Threat; Antimicrobial Resistance (AMR): -The Importance of Clinical Testing to Protect Japan-

Growing Awareness of Antimicrobial Resistance

Antimicrobial resistance refers to a resistance to antibiotics that results in a lack of efficacy or difficulty in achieving efficacy. In 2010, several patients contracted and died in a university hospital from an infection with multiple drug-resistant bacteria. This incident was widely publicized, making the general public more aware of antimicrobial resistance.

In 2013, the U.S. Centers for Disease Control and Prevention (CDC) announced that drug-resistant bacteria are a threat to humans. In the U.S., more than 2 million people are infected with drug-resistant bacteria annually and around 23,000 of these cases result in death. In 2015, a national action plan that aimed to provide a direction for resolving the issue of drug-resistant bacteria was released. The World Health Organization (WHO) advocated the concept of “One Health (living in one world)” in 2014, stating that the existence of drug-resistant bacteria is not only a problem in the limited space of hospitals, but also an issue that should be considered from perspectives that include the whole external environment, including humans and animals (domesticated animals, poultry, pets, etc.).

Because of this global trend, academic societies, administration, and companies in Japan collaborated to set up a committee called the Drug Discovery Promotion Council to provide necessary advice to citizens, the administration, research institutes, and other bodies.

At the 42nd G7 Summit (Ise-Shima Summit), the Council of Cabinet Ministers for Countermeasures Against Infectious Diseases announced an action plan to enable Japan to exercise leadership, which had a great impact. The plan provided directions for six areas,

including enlightenment/education, surveillance, enhanced countermeasures against infection, proper use of antibiotics, promotion of drug discovery, and international cooperation. It also set numerical targets for each area. Based on this, Japan emphasized at the Ise-Shima Summit held in May that it would exercise leadership on the issue of antimicrobial resistance domestically and internationally, especially within Asia.

Emergence of a “Nightmarish” Drug-Resistant Bacteria

Drug-resistant bacteria are constantly evolving and new bacteria are emerging. Carbapenem-resistant enterobacteria (CRE), which the CDC calls a “nightmare bacteria,” is becoming increasingly problematic. CRE is difficult to eradicate because even the most powerful antibiotics do not work for CRE infections. Patients infected with CRE have already been identified in Japan, and in 2014, it became mandatory to notify public health centers if a CRE infection occurs. It is said that this infection is expanding mainly in nursing facilities.

Another recently controversial issue is Clostridium difficile infection. This infection is caused by a bacterium called Clostridium difficile in the intestines that abnormally propagates in response to antibiotic treatment and induces symptoms such as diarrhea. It is considered difficult to treat this infection because most antibiotics do not work on it.

The action plan also set a numerical target to reduce the usage of antibiotics. What we must note here is that the numerical target should not be used on its own. Patient status should be carefully examined to decide on antibiotic use.

Diagnostic techniques are also advancing. Immunochromatography, which can diagnose diseases in as fast as 15 minutes, genetic diagnostic techniques such as multiplex, LAMP and Gene Xpert, and various other diagnostic methods have been developed. In particular, the LAMP method was developed in Japan and is attracting attention as an innovative technique that can visually judge bacteria. However, these methods still have some cost and other issues that need to be resolved. Further development is anticipated.

The incidence of infectious diseases in Japan is much lower than that of other Asian countries. In other words, drug-resistant bacteria are successfully controlled in our country, so we should share our experience and skills with Asia and the rest of the world for the future.



Department of Microbiology and Infectious Diseases, Faculty
of Medicine, Toho University
Professor
Dr. Kazuhiro Tateda

Graduated from Nagasaki University School of Medicine in 1985. Joined the Second Department of Internal Medicine, Nagasaki University School of Medicine in 1985. Studied in the Department of Pulmonary and Critical Care Medicine at the University of Michigan in the U.S. in 1999.

Worked as Associate Professor in the Department of Microbiology and Infectious Diseases, Faculty of Medicine, Toho University in 2005 before assuming his current post in 2011. President of the Japanese Association for Infectious Diseases since April 2017.

Direction of Policies for Medical Devices

Proper Usage After Approval

One of the major roles of the Ministry of Health, Labour, and Welfare is regulatory administration. We tend to imagine from the term “regulation” that free and fluid industrial growth may be hindered, but in fact, a healthy industry is fostered by appropriate regulation. I believe that regulatory administration is essential for developing a strong Japanese industry.

However, regulatory administration also has various problems. Approval reviews in Japan are said to be rigorous for both medical devices and drugs, but once approved, subsequent regulation is pretty loose. Drugs can be used by anyone and can be used in large amounts, and all this usage is covered by insurance. This is because decisions after approval are basically left to the discretion of clinics.

Recently, there was a TV program that could have misled viewers into believing that sleep medicines work for diabetes. Misleading programs like this one are problematic. Also, addictive drugs, such as sleep medicines, should be used carefully. We must further think about proper regulation after approval, especially regarding proper usage, in the future and we must work on this issue promptly.

Optimization of Regulation Before and After Launch

We sometimes receive criticism that Japanese drugs and medical devices are expensive, and that companies profit too much. However, this is not the result of unfair profits made by companies, but often the result of the enormous costs spent on development. To lower prices, development costs should be cut and reviews should be accelerated. At the same time, innovation must be promoted. You may doubt that this is really possible, but we believe that it can be done.

We have various methods for this. The first step may be to strengthen support at the development stage. At the last stage of approval, companies complete clinical studies and finalize data. If their accomplishments are overturned on the brink of approval, companies face a lot of trouble. It would be better to have communication between the authorities and companies from an early stage before approval in order for better products to be developed. With this new idea, we are making efforts to enhance our consultation service.

The balance of regulation before and after marketing must also be reconsidered. If data can be collected after marketing, requirements before marketing may be minimized to lessen burdens. We think that development costs can be reduced by collecting post-marketing data adequately.

We also aim to further streamline the review process for medical devices. Whether or not clinical studies are necessary is controversial, but it is also true that this puts a heavy burden both on the healthcare side and the patient side. We would like to make an attempt to boldly overhaul this process and turn it into a more reasonable one.

Aiming to Become a Reference Country

In 2016, a basic plan aiming at the promotion of research and development, or the widespread use of medical devices to improve the quality of healthcare was approved in a cabinet meeting. Some of the main elements of this plan are introduced below.

The first is to develop advanced medical devices based on advanced technologies. This aims to develop medical devices that utilize genomic medicine or artificial intelligence (AI). The situation of AI is still unpredictable because a large gap still exists between the expectations and reality.

The second is to help the growth of venture firms involved in development. Venture firms have professionals in management and finance, but they often lack skilled personnel in pharmaceutical affairs and insurance. This leads to difficulties in obtaining approval. We would like to establish an organization that can alleviate this situation.

The third is to manage medical device regulation smoothly. Guidance on the number of subjects required in clinical studies will be drawn up early in the next fiscal year.

The fourth is to improve the environment to promote global business development. Currently, we are accepting applications for Sakigake designation.

What is worthy of attention in the budgets for the next fiscal year is the budget related to global strategies. As it is believed that review and evaluation methodologies for medical devices in Japan can become global standards, a council secretariat was set up in the ministry. A budget was approved for this project, allowing us to attend and make proposals in international conferences in the future. Even though the future of the health administration is unpredictable partly due to the inauguration of the Trump administration in the U.S., we always keep an eye on global strategies. Ultimately, our country will aim to become a reference nation.

Owing to the postponement of the consumption tax hike from 2017 to 2019, financial resources are limited. However, the healthcare system must be maintained regardless of the environment. The situation will remain uncertain for the next few years. Nevertheless, cutting development costs, avoiding excessive burdens on health insurance, promoting innovation, and putting the priority on patients are unalterable themes that we have to honor, regardless of whether or not we have the funds.



Director-General, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Mr. Toshihiko Takeda

Graduated from The University of Tokyo Faculty of Law in 1983. Joined the Ministry of Health, Labour and Welfare in the same year. Appointed as a planner in the Health Policy Bureau in 2000 to take charge of the healthcare area. Worked as a councilor for the integrated reform of social security and tax system. Worked as a minister's secretariat, director-general, etc. in the Ministry of Health, Labour and Welfare before assuming his current post in June 2016.

Patient's Voice

Treatment Methods and Future Challenges for Pediatric Brain Tumors



Pediatric Brain Tumor Network
Ms. Yuko Moue, Representative

Pediatric brain tumors have the highest mortality among pediatric cancer, which is the leading cause of childhood disease death in Japan. Of about 2,500 estimated pediatric cancer cases per year, around 500 are said to be brain tumors, which makes them the second-most common cancer after leukemia. As more than 100 types exist for pediatric brain tumors, this disease can be considered as a group of many rare diseases.

Chemotherapy and radiation therapy are more effective for children than for adults, and so treatment of pediatric brain tumors has significantly advanced in the past decade for some diseases, such as medulloblastoma. In contrast, some diseases including pediatric diffuse intrinsic pontine glioma still have no definitive treatment, and unfortunately, the prognosis of such diseases worsens a short time after onset. Widely different treatment methods are selected for pediatric tumors according to the age, tumor site, and grade. For example, high-dose chemotherapy is used rather than radiation therapy because it has become known that children who receive radiation therapy at the age of 3 years or younger are left with an intellectual disability. This means that multidisciplinary treatment in related clinical departments is in high demand. Brain surgeries, strong drug therapies, and radiation therapies for children in the growth and development period cause motor, endocrine, and psychiatric disorders, and many other problems, as well as a number of sequelae and late complications. More than a few patients are forced to spend their whole life having difficulties in daily life.

It is also difficult to make a differential diagnosis from symptoms of common pediatric diseases, such as nausea, headache and double vision, and in some cases, patient families visit various departments including pediatrics, ophthalmology, otolaryngology, and psychiatry, but the disease is still not diagnosed until it has progressed. There is a strong need to enlighten primary care physicians through education on pediatric brain tumors, development of innovative diagnostic devices or tools, and healthcare collaboration, so that diseases can be detected early.

Isolating a brain tumor damages the brain, but recently a large number of new medical devices and technologies, such as navigation systems, mapping, awake surgery, intraoperative fluorescence diagnosis, and intraoperative MRI, have been put to use to isolate the necessary sites accurately and minimize damage. Proton beam therapy for pediatric solid tumors was covered by insurance last year. Functions to improve treatment, and reduce sequelae and complications are strongly desired in the development of various radiotherapy devices and new medical devices.

Patients cannot readily know what kind of advanced medical devices are required for their disease and where they can find them. I strongly hope that future advances in medical devices and diagnostic technologies will become more understandable and quickly

selectable by patient families, which will help to make a significant improvement to the cure rate and QOL of children.

Pediatric Brain Tumor Network : <http://www2.pbtn.jp/>

Voice from the Local Government Expectations for the Medical Device Industry — For Creation of Innovation — Chiba Prefecture



Director of Healthcare Division
Dr. Shigekazu Komoto

1. Challenges Faced by Local Governments

Shortage of physicians, nurses, care staff, and childcare workers.

The largest challenge faced by local governments in Japan is the shortage of human resources. According to recently published vital statistics from the Ministry of Health, Labour and Welfare, about 977,000 children were born in 2016, falling below 1 million for the first time since 1899 when the statistics were first collected. This news surprised me.

Amid a shrinking workforce, the number of hospitalized patients and home-care patients is expected to increase 1.4-fold and 2-fold, respectively, in Chiba Prefecture. In the labor-intensive industries of healthcare and nursing care, more human resources are required as the services provided increase and become more sophisticated. As a result, the issue of a shortage of human resources remains unsolved, possibly bringing about obstacles in the safety of healthcare, especially in rural areas. Construction of a safe and secure society based on the rapidly declining and super-aging population is required.

2. Innovation Wanted

I expect innovation for the medical device industry, including AMDD, to overcome this hardship. In other words, I would like to ask you to develop devices that can realize healthcare and nursing care of higher quality, and a happier society despite fewer people in the workforce.

Dr. Hiroshi Yoshikawa, Professor Emeritus at The University of Tokyo, said that, in the postwar years of high-speed economic growth during which the Japanese economy grew by 10% per year in real terms, the workforce increased by only 1.3% per year, and the difference of about 9% was due to higher labor productivity. Why don't we aim to improve labor productivity through innovation, not through selfless devotion, for our children's future?

3. An Eye on the Entire Community

Healthcare and nursing care will become increasingly borderless. Out of the total of about 1,700 municipal areas in Japan, a trial-and-error process is underway to shift from the traditional hospital-centered healthcare to comprehensive local care in which the entire community provides healthcare and nursing care. Efforts for prevention and early detection are also important.

Why don't you create innovation using your knowledge, skills, experience, and vitality in the field of the world's most advanced aging society, not only in operating rooms, laboratories, and hospitals, but also with an eye on the entire community?

4. Three Appealing Points of Chiba Prefecture

Chiba Prefecture, which encapsulates Japanese society, is the best environment for proof of concept in medical device development. The prefecture is also promoting collaboration between medicine and engineering, and will utilize the advantage of being designated as a strategic special zone to support your business in medical device development. If you are interested, please call the Investment Promotion Division, Commerce, Industry and Labor Department (+81-43-223-2444).

[1] It has an enriched road network including the Tokyo Bay Aqua Line and Metropolitan Intercity Expressway, and easy domestic and international access through Narita Airport and Chiba Port.

[2] In addition to various industrial areas, including Kazusa Akademia Park and Chiba New Town, new technoparks are being built in Sodegaura and Mobarra. A variety of support programs are available for new plants and laboratories.

[3] Advanced medical institutions in healthcare, AI, etc. including The University of Tokyo Kashiwa Campus, National Cancer Center Hospital East, Chiba University, Chiba Institute of Technology and Kazusa DNA Research Institute are located there.

AMDD Co-Sponsored the Japan Medical Association/AdvaMed Joint Symposium

The American Medical Devices and Diagnostics Manufacturers' Association (AMDD) co-sponsored the joint symposium of the Japan Medical Association and Advanced Medical Technology Association (AdvaMed) entitled "Vibrant Nation: Realizing the Fullness of "Ikigai" in Japan, The Role of Health Innovation in Delivering Growth, Productivity, and Cost Savings." held on April 26. The symposium was held to mark the publication of the Japanese version of a U.S. report on the economic effects of advanced medical devices. After speeches by Dr. Yoshitake Yokokura, President of the Japan Medical Association, Mr. Shuji Shirakawa, Deputy Chairman and Director of the National Federation of Health Insurance Societies, Mr. Ichiro Kamoshita, Chairman of the Parliamentary Association for Quick and Safe Access to Superior Medical Devices, and Mr. Kozo Yamamoto, Minister of State for Regional Revitalization and Regulatory Reform in the Cabinet Office, Mr. Ross DeVol, Chief Research Officer at the Milken Institute, U.S., who prepared the report, provided a keynote lecture.

In the subsequent panel discussion on current healthcare from the perspectives of physicians, the administration, and patients, the motivation in life beyond QOL from their the different viewpoints was discussed.



(From left)

(Moderator) **Dr. Shuzo Nishimura**, President, Institute for Health Economics and Policy

Dr. Yuichi Murayama, Chief Professor, Department of Neurosurgery, The Jikei University School of Medicine

Dr. Yasuo Terauchi, Professor, Department of Endocrinology and Metabolism, Yokohama City University School of Medicine

Dr. Yasuhiro Suzuki, Director-General, Health Insurance Bureau, Ministry of Health, Labour and Welfare

Ms. Yumi Kagawa, Chief Director, NPO Kanja Speaker Bank

AMDD Held the General Meeting

The American Medical Devices and Diagnostics Manufacturers' Association (AMDD) held the 8th General Meeting on March 15. After an opening speech by Chairman Kosuke Kato, Managing Director of Edwards Lifesciences Corporation, the settlement of account in 2016 was closed and the budget for 2017 was unanimously approved. In a special lecture, Mr. Toshihiko Takeda, Director-General of the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare was invited to make a speech entitled "Direction of Policies for Medical Devices." The participants asked many questions about his passionate lecture, making for an invaluable time for both sides. (See page 2 for summaries of the lecture by Mr. Takeda)

The Value of Medical Technology

<Diagnosis and Treatment of Cancer>

Evolution of Laparoscopic Surgery: Cancer Surgery Without Opening the Abdomen

In recent years, laparoscopic surgery, which minimizes lesions, has become increasingly common. Unlike a traditional laparotomy, laparoscopic surgery is a type that inserts a camera and operation device through a small hole opened in the abdomen and removes lesions while the surgeon consults a monitor. Various devices have been developed to enable the surgeon to operate through a hole as small as 1 or 2 cm in diameter. In particular, the evolution of energy devices that coagulate and cut tissues while suppressing bleeding is astonishing. In 2016, an ultrasonic coagulotomy device that can treat blood vessels no larger than 7 mm in diameter was developed and has been used by surgeons. The



usage of automatic suture devices that automatically cut lesion sites in the stomach or large intestine has also been practiced by many people, and now, all procedures including anastomosis (a procedure to connect tissues after cancer removal) can be completed in the body cavity.



We have high hopes that there will be continued improvement of clinical values through new device development and contributions to surgeons and patients through the realization of less invasive procedures. (Article written with full responsibility by Masakazu Hirata, Ethicon Division, Johnson & Johnson K.K.)

AMDD Held 6th Joint Media Seminar with JACRI — A Global Threat; Antimicrobial Resistance (AMR): Importance of Clinical Testing to Protect Japan —

The Japan Association of Clinical Reagents Industries (JACRI) and American Medical Devices and Diagnostics Manufacturers' Association (AMDD) held the 6th joint media seminar at the JA Building Conference in Otemachi, Tokyo on February 22, 2017.

Dr. Kazuhiro Tateda, Professor, Department of Microbiology and Infectious Diseases, Faculty of Medicine, Toho University was invited to provide a lecture on the current situation of AMR in the world and Japan, importance of clinical tests and future challenges to be addressed under the theme of “A Global Threat, Antimicrobial Resistance (AMR): Importance of Clinical Tests to Protect Japan.”



Dr. Kazuhiro Tateda

In the opening speech, Mr. Tetsuya Teramoto, President of JACRI, said that a strategy against infectious diseases and antimicrobial resistance has been recently focused on as an urgent issue. He mentioned that an action plan against antimicrobial resistance was adopted also in Japan in April 2016, and in this action plan, a concept of “One Health” to implement measures in a way that goes beyond the boundary of humans, animals and the environment is especially important.



Mr. Tetsuya Teramoto,
President of JACRI

Materials on clinical reagents for antimicrobial resistance were exhibited at the back of the venue which attracted the media's attention.

(See page 1 for summaries of the lecture by Dr. Tateda)

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.