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The History of Neuroscience and Neurosurgery in Japan

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1. iPSC and Parkinson Disease (PD)

iPSC technology has opened the door to a new field of cell reprogramming and regenerative medicine. Human iPSCs can provide a promising source of midbrain dopaminergic (DA) neurons for cell replacement therapy for PD. It has become possible that DA neurons are efficiently induced from iPSCs without contamination of remnant undifferentiated iPSCs. Still there could be a risk of slowly-growing tumor formation and graft-induced dyskinesia, but great efforts are being made towards clinical application of iPSCs for patients with PD. In addition to PD, the iPSC technology is applied to a wide variety of intractable diseases such as retinal degeneration, spinal cord injury and stroke (4, 5). Another notable clinical research on going in Japan in the field of regenerative medicine is intravenous administration of bone marrow stromal cells for patients with cerebral stroke, obtaining promising results (6). The stem cell-based regenerative medicine will become one of the important fields in neurosurgical treatment in future.

2. Microneurosurgical Anatomy

As widely recognized contribution of Dr. Albert L. Rhoton to the development of modern neurosurgery has been extraordinary, especially as the pioneer of microneurosurgical anatomy. He has intensely studied in this field over the past 40 years. His book published in 2007 titled "Rhoton Cranial Anatomy and Surgical Approaches" is a compilation of his publications related to this field (7). He lists in the foreword of the book all research fellows who have worked with him in his laboratories; more than one-third of them are Japanese, the biggest number of researchers from single countries. I (S.K.) was fortunate to work with Dr.Rhoton at Mayo Clinic and helped him to publish in 1968 one of his earliest papers on microsurgical anatomy dealing with the nervusintermedius of the 7th cranial nerve (8). The Rhoton's book covers almost entire areas of the central nervous system except probably for spine which will need to be studied.

It is noteworthy that the Japanese Society for Microsurgical Anatomy (initially under a different name) was founded in 1986, majority members of which had studied at Rhoton's laboratory at the University of Florida, later joined by colleagues who studied with Drs. Ossama Al-Mefty and Takanori Fukushima at their respective laboratories in U.S.A. The Society has published 20 volumes of the proceedings of its yearly meetings since (9). This is believed to have contributed to improving neurosurgical procedures and their standardization in Japan.

As future perspectives in the field of micro-neurosurgical anatomy, several developments are expected. One is the work applicable to recently developing fields such as intravascular surgery and image analyzing technology. Secondly, microsurgical anatomy is helpful not only for surgery, but for development of diagnostic imaging studies with various modalities. Thirdly, as surgical anatomy is directly related to surgical approaches and procedures, how to teach and train young neurosurgeons is important, necessitating further development of effective means such as 3D simulation tools (10). Other perspectives would include elucidative laboratory study with bloodless cadaveric specimens on subjects already proposed from surgical experience (11), and reviving traditional anatomical studies in trying to apply to new surgical procedures on the basis of advanced knowledge (12). Seeing the fast developing endoscopic surgery in recent years, anatomical study specific for this field would be awaited. It should be noted that during the course of laboratory study on surgical anatomy, new approaches and surgical categories could develop, like finding the cerebellomedullary fissure to have opened an approach to the 4th ventricle without sectioning the vermis (13), and proposal of entry zones to the brainstem to have initiated a new concept of direct approach to parenchymal legions of the brainstem (14). Important recent papers on

microsurgical anatomy by Japanese include those on bypass surgery and transclival approach (15-17).

3. Research and Clinical Studies on Intracranial Aneurysm

Japanese neurosurgeons have made great efforts regarding intracranial aneurysms, as the incidence of subarachnoid hemorrhage following rupture of aneurysms in Japan and Finland are known to be the highest among different countries. The results of demographic studies on subarachnoid hemorrhage in rural communities such as Hisayama and Izumo were reported in the 1990s (18-20), while Hashimoto et al. succeeded in experimentally inducing aneurysms in rat brain 1978 (21). With a unique diagnostic trend of brain screening study in Japan popularized, preventive treatment of unruptured intracranial aneurysms against natural course has become a focus of study (22-26). A large scale study had to wait until the ISUIA which reported extremely low risks of rupture in small sized aneurysms, while risks of treatment were high (27). Many studies were made in Japan, but they were small in scale and in addition they were retrograde studies, making it difficult to determine the definitive indication for their treatment. Several retrospective studied were made and finally a large scale prospective national study UCAS Japan was conducted under the auspices of the Japan Neurosurgical Society (28-30).

4. Current Status of Studies in Japan

4.1. Clinical Study

4.1.1. UnrupturedAneurysms: Risk of Rupture vs. Natural Course

Ishibashi et al. from Jikei University reported the result of prospective study on unruptured aneurysm of 529 (419 patients) from their university (28). Overall rupture rate was 1.4% with the size, subarachnoid hemorrhage and posterior circulation as influencing factors. Of notable finding was that with regard to small sized aneurysms, the number of cases with subarachnoid hemorrhage exceeded that of unruptured by 5.5 times. Sonobe et al. followed prospectively 448 aneurysms (375 patients) smaller than 5mm without treatment (SUAVe study) (29). During the observation period of 1306 person-year, rupture occurred in 7 patients (0.54%/year ;95% CI:0.2-3%); In 30 aneurysms (25 patients) showed an increase in size by greater than 2mm. Factors influencing rupture included multiplicity, hypertension, size greater than 4 mm and the age older than 50 years. As factors influencing enlargement were the size greater than 4mm, female, multiplicity and smoking. This report is noteworthy as a less biased study without treatment.

UCAS Japan was reported in 2012 (30).This study was conducted in 283 neurosurgical institutions in Japan dealing with 6697 aneurysms (5720 patients) registered during 2001 to 2004. Patients were prospectively enrolled. The results were obtained from observation of 6697 aneurysms (5720 patients) and 11660 aneurysm-year. Rupture occurred in 111 aneurysms with yearly rupture rate of 0.95%. Influencing factors were the size, location (especially anterior and posterior communicating arteries) and form of aneurysm. In this study larger aneurysms were found in elderly patients. In 2014, Dutch group made a meta-analysis of 6 prospective cohort studies including ISUIA and the above Japanese studies. They developed PHASES Score for prediction of the risk of rupture of aneurysms (31). Risk factors they extracted were race (Japanese and Finish), hypertension, year, size, history of subarachnoid hemorrhage, location (anterior cerebral artery, posterior communicating artery and posterior circulation). This study proved first time on the basis of prospective meta-analysis that aneurysms in Japanese tend to rupture 2.8 times more than those in western races.

4.1.2. Analysis of the Risk of Aneurysm Rupture by Computer Flow Dynamics (CFD)

CFD has been applied to analyze various risk factors concerning rupture of aneurysms in clinical cases since around the turn of century. In 2004, Shojima et al. from Tokyo University reported first in the world that the sheer stress of ruptured middle cerebral artery aneurysms was low (32), followed by Miura et al. from Mie University (33). The possibility of intra-aneurysmal pressure relating rupture has recently been suggested.

4.1.3. National Registration Studies on Endovascular Therapy for Unruptured Aneurysms

Multi-center studies on endovascular treatment for unruptured aneurysms (JR-NET, JR=NET2) were conducted in Japan with participation of 122 institutions, reporting the results in 2013(34). A total of 4767 aneurysms (4573 procedures) were treated between 2005 and 2009; 57.7% of the aneurysms were completely embolized, 2.1% could not be embolized. More than half of aneurysms smaller than 10mm had a wide neck, necessitating complex procedures. Complication rate was 9.1% which was seen more in aneurysms larger than 20mm, in the posterior circulation and with wide neck; intraoperative hemorrhage occurred significantly more in aneurysms smaller than 3mm. Lowering of Modified Rankin Scale greater than 1 occurred in 2.12% and death in 0.31%.

4.2. Basic Studies

4.2.1. Medical Treatment for Aneurysms

Aoki et al. of Kyoto University reported that in experimental aneurysms, enlargement of aneurysms was suppressed by oral intake of statin (35, 36), suggesting the possibility of its clinical use for growth suppression and rupture prevention. In a case control study of patients with subarachnoid hemorrhage and with unruptured aneurysms, Nozaki et al. reported statin intake rate was

greater in patients with subarachnoid hemorrhage (37). Hamamatsu and Osaka groups reported that periodontitis with a certain streptococcal infection tended to cause subarachnoid hemorrhage and intracerebral hemorrhage (38); a large scale study is currently conducted in an attempt to elucidate the relation.

4.3. Future Prospects

Rupture of intracranial aneurysms is encountered in Japanese population so frequently, making it an important issue for Japanese neurosurgeons to cope with. Screening attempts to find cerebrovascular diseases and other brain pathology started in Japan as "Brain Dock". This prompted to conduct various basic and clinical studies regarding unruptured aneurysms among general population, which have provided valuable information to the world as a top runner in this field. As clipping operation for both ruptured and unruptured aneurysms tends to be much less frequently performed over the world, obtaining aneurysmal specimen at surgery would be extremely difficulty except in Japan, lessening the chances of its study. The answer as to why the risk of rupture among Japanese is so high is yet to be determined.

5. Surgery for Cerebral Ischemia

Preventive effects of endarterectomy for severe stenosis of the internal carotid artery on onset or recurrence of strokes have already been established by many randomized controlled trials. Cerebral hyperperfusion syndrome was first reported as a complication of carotid endarterectomy (CEA) by Professor Sundt, as occurring in relation to cerebral edema or intracerebral hemorrhage (39). Japanese neurosurgeons' reports to clarify its pathophysiology include 1) reactive oxygen species produced during intraoperative transient ischemia due to carotid cross-clamping in addition to preoperative cerebral hemodynamic impairment correlate with development of cerebral hyperperfusion after CEA (40), 2) preopeative cerebrovascular reactivity to acetazolamide measured using neuroimaging predicts development of cerebral hyperperfusion after CEA (41), and 3) strict control of blood pressure immediately after surgery prevents development of intracranial hemorrhage due to cerebral hyperperfusion syndrome (42).

Studies by Japanese researchers in the 1990s demonstrated that misery perfusion, detected by PET (positron emission tomography) or SPECT(single-photon emission computed tomography) with acetazolamide challenge, is a predictor of subsequent stroke in medically treated patients with symptomatic major cerebral arterial occlusive diseases (43-45). A recent study from Japan also showed that misery perfusion is still a predictor of subsequent stroke despite recent improvements in medical treatment for secondary prevention of stroke and the predictive value of misery perfusion has not changed in recent years (46). Whereas a randomized controlled trial in the United States demonstrated no benefit of arterial bypass surgery for such patients (47), the Japanese extracranial-intracranial arterial bypass surgery trial has showed that the surgery is beneficial for patients with symptomatic hemodynamic cerebral ischemia due to major cerebral arterial occlusive diseases (48). The difference between the results of the two studies may be due to pre- and post-operative management rather than failure of intraoperative procedures. Japanese neurosurgeons have continued to investigate pathophysiology of chronic cerebral ischemia in atherosclerotic cerebrovascular steno-occlusive diseases and moyamoya diseases, resulting in reduction in perioperative complications in patients undergoing arterial bypass surgery.

6. Glioma

Treatment of brain tumor in general have made a remarkable improvement with refinement of intraoperative monitoring and introduction of new surgical techniques and approaches. However, the results of treatment of glioma, especially glioblastoma is still not favorable. As the use of new chemotherapeutic agents were approved by the government recently in Japan, temozolomide in 2006, and bevacizumab, gliadel and 5-aminolevulinic acid in 2013, the therapeutic results are expected to improve together with the induction of awake surgery and intraoperative MRI. The problems with glioblastoma treatment include that half of the patients have Karnofsky Performance Score at 70 or less at the time of tumor detection, half of the patients are over 60 years of age, and only about 60% of the patients are amenable for gross total resection, and effective chemotherapeutic drugs are not enough. In the present, 5-year overall survival rate is estimated to be about 15% in Japan.

6.1. Genomic Analysis

A remarkable progress in glioma research has been made for genomic analysis in the past 10 years, such as by TCGA (The Cancer Genome Atlas). Notable progresses include establishing measurement of genomic methylation of MGMT(O6-methylguanine DNA methyltransferase) promoter as a predicting factor for the effect and prognosis of temozolomide, and detection of IDH1/2 (Isocitrate dehydrogenase 1/2) gene mutation pertaining to the prognosis of glioma. A new brain tumor translation research section in the National Cancer Center of Japan was opened in 2012 to coordinate gene study across the country.

6.2. Brain Tumor Registry

Brain Tumor Registry of Japan published in 2014 a report on data from the entire Japan on the basis of the WHO brain tumor classification. It includes the overall survival time, progression free time as well as 5-year survival rate of all brain tumors, which are edited for practical use at bedside. Detailed follow-up data including rare brain tumors will be obtained under anonymity design. A higher quality data regarding all brain tumors will be available

by combining nationwide Cancer registration which will take place in 2016 with the National clinical data and DPC (Diagnosis Procedure Combination) database,

6.3. Japan Clinical Oncology Group (JCOG)

JCOGis the largest study group dealing with tumors in Japan; the Data Center is located in the National Cancer Center. Clinical research has been conducted on various subjects including glioblastoma, grade II-III gliomas, primary central nervous system lymphoma and brain metastases. Gene analysis of the patients enrolled in the studies is expected to produce answers to biological problems of the diseases (49-56).

7. Intraoperative Electrophysiological Monitoring and Brain Function

There are two modalities for intraoperative direct evaluation of brain function: one is with awake surgery and the other electrophysiological monitoring. Study on focal brain function by electrical stimulation in awake state was pioneered by Penfield (57) and later systematically studied by Ojeman(58). Awake surgery, however, was never widely used as it caused pain to patients. Brain mapping by placing subdural chronic electrodes was utilized to determine the extent of brain resection with the resection performed at a second surgery. However, it is invasive and also subcortical neural structures cannot be evaluated by this method. Then, introduction of intravenous anesthesia with propofol enabled evaluation of brain function with patients in sedated awake state. This anesthesia is presently widely used and has proved to be useful, especially for glioma surgery.

Awake surgical techniques were introduced into Japanfrom western countries and has made a unique development. We know linguistic differences between Japanese and western languages in that, for instances, Japanese isa vowel dominant language while western languages consonant. Speech centers for both languages are similar in location with regard to dominant hemisphere and Broca's area, but detailed language functions may be different in location and complicated when considering those functions as auditory perception, phonation, and comprehension of letters and sentences. Studies on locational differences among different languages will be made in future by accumulating further experience with awake surgery and studies with various modalities on normal subjects.

With regard to intraoperative electrophysiological monitoring, sensory evoked potential (SEP) and auditory brainstem response (ABR) have long been used. However, intraoperative use ofmotor evoked potential (MEP) had been awaited as it would correlate more directly with postoperative state of motor function. One of the difficulties concerned anesthetic effects. The problem was solved with introduction of intravenous propofol anesthesia; MEP recording is now widely available. Japanese contributions to this field include development of high frequency stimulation (59) and refinement of spinal D wave monitoring which theoretically enables quantitative evaluation of the pyramidal tract function (60).

Both awake surgery and intraoperative electrophysiological monitoring aim at preserving the neurological function of patients after surgery. These procedures are to help decide where to stop tumor resection on the basis of the present neurological status in order to preserve function. it is expected to study further on the extent of tumor removal with consideration on plasticity of the brain by which functional regaining could develop in the postoperative course (61). Research may also be made in future on restoration of brain function by technologies of iPSC and/or brain-machine-interface (BMI). Neurorehabilitation is important at present and in the future. Rehabilitation in conjunction with noninvasive brain stimulation (NIBS) techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) may be promising (62).

8. Diagnostic Neuroradiology

8.1. CT and MRI will be Mentioned Representing Diagnostic Radiology Devices

8.1.1. CT

As CT was introduced in the latter half of the 1970s, it rapidly spread widely. Helical CT and multi-slice CT scanners were developed in the 1990s and around the turn of century, respectively. Much of the development and marketing of those CT scanners owes Japanese CT makers, especially Toshiba Co. Professor Katada K of Fujita Health University participated intensely these development. The latest cutting edge model enables 4D scanning of 16cm width using 320 multi-slice CT scanner, enabling to scan and store the data of the whole brain as short as in 0.3 sec. It also has a specification to obtain CBV with multidimensional CT angiogram (4D CTA or 3D CT DSA). Many studies have been reported from Japan on CTA, with special respect to aneurysms (63, 64). Recent topics include simultaneous analysis of hemodynamic and perfusion study, and CTA simulation of cerebral blood flow.

8.1.2. MRI

MRI was rapidly popularized since superconductive MRIs were introduced in Tokyo and Kyoto Universities in 1984. At present, the number of MRI per population in Japan is the greatest in the world. Progress of MRI was seen in MRA and Fast SE (Spin Echo) around 1990, functional MRI and diffusion MRI (DWI) by EPI (Echo Planer Imaging) in the middle of the 1990s, SENSE (parallel imaging) and true FISP around 2000, and thereafter 3T MRI, perfusion MRI, diffusion tensor imaging (DTI), susceptibility weighted image (SWI), arterial spin labeling (ASL), 7T MRI and so forth. As to Japanese contribution, Ogawa S proposed first time the BOLD (Blood oxygen-

ation level-dependent) effect in fMRI (65) and technological contribution was made in Fast SE method by Oshio K, DTI tractography by Masutani Y (66), and ASL (Arterial Spin Labelling) by Kimura H. Japanese machine makers' contribution is not as great as for CT but produced such unique systems as cisternography and CSF flow measurement.

Clinical papers from Japan related to MRI are abundant as it is so widely installed. As to more basic studies, study on aging of the brain from data of widely practiced brain screening examinations (Brain Dock) (67), a unique study combining tissue engineering and DTI, and an MRI study on marmoset brain (68) are of note. There are unique clinical research papers from Japan including a report by Fujisawa I et al. from Kyoto University on the posterior lobe of the pituitary gland (69), paper on dissecting aneurysms of vertebrobasialar arteries, B-PAS (Basi-Parallel Anatomical Scanning) by Nagahara M (70), intraarterial signal of FLAIR, cisternal signal in moyamoya disease, DWI and cellularity (71), statistical analysis of MRI in Alzheimer disease, and more recently an enhancing effect of the cochlea in Meniere disease (72).

9. Stereotactic radiosurgery

The gamma knife stereotactic radiosurgery (GK-SRS) device was installed in Tokyo University in 1990, making it the first in Japan. The GK has since spread to 54 hospitals across the country. The total number of GK treated patients in Japan had reached 18700 by 2012, while the global total was 74200. Linear accelerator (LINAC) SRS and SRT (stereotactic radiotherapy) devices are now available in almost all hospitals in Japan performing conventional radiation therapy. In Japan, 12 institutions, the largest number in one country, have installed a cyclotron using particle beam SRS and SRT. SRS for brain metastases is performed more aggressively in Japan than in other countries. For instance, the disease most frequently treated with GK-SRS is brain metastasis (70%), followed by benign tumors (20%), vascular disease (8%) and, infrequently, functional disorders (2%).

Three milestone studies have been conducted on SRS in Japan, one for arteriovenous malformations (AVM) and two others for brain metastases (73-75). The AVM study, conducted by Maruyama et al. in 2005 (73), showed that SRS significantly decreased the risk of hemorrhage in AVM patients, even before angiographically-confirmed complete obliteration. The second study was a randomized controlled trial (RCT) conducted by Aoyama et al. (Japanese Radiation Oncology Study Group, JROSG 99-1 study) in 2006 (74). They allocated patients to a whole brain radiation therapy (WBRT) plus SRS arm and to a SRS alone arm, and found no significant difference between the two arms. This study proved the efficacy of both protocols for 1-4 small (≤3cm) brain metastases, providing level I evidence. The third study, the Japanese Leksell Gamma Knife (JLGK) 0901 conducted by Yamamoto et al. in 2014 (75), had a prospective multicenter design and examined GK-SRS alone for 1-10 brain metastases. This study proved the non-inferiority of GK-SRS alone in 208 patients with 5-10 brain metastases, as compared to 503 patients with 2-4 lesions. Their results support GK-SRS alone treatment for 5-10 brain metastases with level II evidence. Several retrospective studies and one RCT (Japanese Clinical Oncology Group, JCOG 0504) are now underway. The JCOG0504 study allocated patients to a surgery plus WBRT arm or to a surgery with observation or SRS arm. The final results will be reported in 2015. Publication of studies from the above and other study groups is expected to further delineate the efficacy of SRS vis-a-vis observation, open surgery and other means of radiation treatment.

10. Innovation of Instruments and Robotic Neurosurgery

In modern neurosurgery, surgery under microscope is routinely practiced. From the point of view of OR armamentarium, innovation of microsurgical instruments and OR setup are important. In this field, among contributions by Japanese neurosurgeons that of Dr. Sugita K. is conspicuous. Sugita clips have a largest share on the market in the world with their excellent characteristics. Professor Sugita made many other important innovations of instruments for microneurosurgery. What he called "Trilogy of microneurosurgery" are operating microscope, table and chair. It is to be stressed that these three devices are operated in a robotic way by the surgeon sitting on the operating table; the surgeon by stepping on buttons on the footplate of the table electrically moves and controls all functions of the microscope including its X-Y-Z motions, focusing and zooming, motions of the chair in all directions and height, and horizontal motions and tilting of the table.

This concept further developed to "robot assisted neurosurgery" to seek accuracy of surgery, fine and smooth motion of instruments without fatigue and concept of remote controlling. With the support of the Japanese government and collaboration with manufacturing companies and universities, surgery performing robot with tele-controlled micromanipulator system was first clinically applied in 2002 at Shinshu University Hospital to a patient with brain tumor; surgery was combined with conventional microsurgery (NeuRobot) (76). The micromanipulator of 10mm diameter was equipped with three micro-forceps and 3D endoscope. The difference from the arm of the da Vinci Surgical system is that NeuRobot enables procedures in the deep brain, while the Da Vinci system with multi-arms, each 10mm in diameter is fitted for a shallower and wider operative field. Further development of surgery performing type of master slave machine following NeuRobot has been suspended in Japan because of difficulties in the process of getting the governmental approval. In the meantime, robotically operated devices such as surgeon's arm supporting device and a robot-assisted tissue holding forceps have been

developed (77). Neurosurgical robotic system akin to the da Vinci concept is being developed for microsurgery in a deep field by Morita (78).

Applying robotic technology or any basic research to clinical use confronts with difficulty and time consuming to go through the governmental approval process. Translational research is a research field to study this process ensuring the efficacy and safety of new innovations and treatments for patients. It is expected that innovation is encouraged and the process is quickened by the current revitalizing strategy of Japan.

11. Stereotactic and Functional Neurosurgery

Stereotactic and functional neurosurgery is one of the oldest sub-specialties in neurosurgery. Even before introduction of stereotactic operations, neurosurgical management of intractable pain, movement disorders, spasticity, epilepsy, and psychiatric disorders was an important field of neurosurgery, because effective medical treatment was not available. In 1947, Spiegel and Wycis first established stereotactic surgery in human, which facilitated accurate operation for deep structures in the brain. Importance of the pallidum and thalamus was recognized in the treatment of involuntary movements, and stereotactic pallidotomy and thalamotomy became very common for treating PD and dystonias in 1960-70s. Professor HirotaroNarabayshi independently invented his own stereotactic device and performed pallidotomy for PD for the first time in the world in 1952.

Stereotactic surgery then dramatically declined because of introduction of L-dopa in the late 1960s. This decline was also accelerated by the socially aggressive movements against psychiatric surgery, and subsequently even against stereotactic and functional procedures, in around 1970 (79). However, Professor ChihiroOhye continued stereotactic thalamotomy for tremor and finally established selective Vim minimal thalamotomy. With introduction of computed tomography in the 1980s, stereotactic surgery became a base of image guided and navigation surgery for mass lesions in the brain. In early 1990s, Laitinen(80) re-discovered that postero-ventrolateralpallidotomy alleviates all the symptoms of PD.

Benabid found high frequency electrical stimulation gave similar effects on tremor with ablation of the Vim nucleus of the thalamus, and established the basis of deep brain stimulation (DBS). In the late 1990s, traditional lesioning stereotactic surgery was almost completely replaced by DBS, and functional neurosurgery entered the era of neuromodulation.

It should be remembered that many common techniques and devices in today's neurosurgery have emerged from the field and concept of stereotactic and functional neurosurgery; neuro-navigation, electrophysiological monitoring, awake surgery, cortical mapping, stereotactic radiation therapy including gamma-knife, neuro-endoscope, minimally invasive surgery, neurotransplantation, neuromodulation and drug pump.

From around 2000, application of DBS started for intractable psychiatric disorders such as obsessive and compulsive disorder and major depression by targeting various structures of the limbic system. After 15-year experience of DBS in PD, some encouraging data for the earlier use of DBS has been shown (81), while it became evident that STN DBS does not prevent natural progression of PD and does not control non-motor symptoms of PD.

However, very long-term stable effects of DBS for intractable dystonia have been established, as the majority of dystonias are not degenerative disorders. Because there is (and will be) no effective medication for dystonia, neurosurgical treatment plays a very important role in the management of dystonias. We are entering in a stage where we can call dystonia "neurosurgical disorder" in terms of treatment (82).

DBS is adjustable and reversible, while it is merely to control the symptoms and does not bring cure to the patients. Therefore, recently, interest in traditional ablative stereotactic surgery like thalamotomy and pallidotomy with modern techniques has been returning. Ablative functional operations are resurging with the use of new techniques such as gamma-knife and focused ultrasound (83). Some neurosurgeons are "hunting" for new indications of DBS such as control of obesity, anorexia, drug addiction, and dementia. Even selective erasing of memory with DBS for post-psych trauma syndrome has been proposed, and memory enhancement is practically not a dream. Such movements have very dangerous aspects in terms of ethical points, which we neurosurgeons have to be well aware of.

There are many old but still useful microsurgical functional procedures that are completely underutilized. These are like "endangered spices", but should not become "extinct species". Selective peripheral neurotomy (SPN) is an excellent procedure for focal spasticity in patients with post-stroke spastic hemiplegia. Considering the total management of patients with cerebrovascular diseases, any vascular neurosurgeons have to be able to perform SPN. Selective dorsal rhizotomy (SDR) is also very important and powerful method for children with spastic cerebral palsy. SDR is one of rare scientifically verified operations with a high evidence level. Every pediatric neurosurgeon has to be familiar with SDR. Microsurgical lesioning of the dorsal root entry zone of the spinal cord is very important for management of intractable pain. The issue is that micro-neurosurgeons are not familiar with management of such seemingly invisible functional disorders, while many functional neurosurgeons are not familiar with visible microsurgical techniques. Professor Marc Sindou in Lyon, who did only microsurgery and did not do stereotactic operations, served as president of the World Society for Stereotactic and Functional Neurosurgery because of his great contribution to functional microsurgery. Any neurosurgeons can start functional neu-

rosurgery from today without using a stereotactic device, but with their brilliant brain.

Professor Leland Albright, pediatric neurosurgeon in Pittsburgh, gave "Matson Lecture" in 2004 (84), and stated, "We need to refocus not on the view under our microscope but on a view outside our present field of vision. I ask again, should we not focus on the disorders (such as epilepsy, cerebral palsy, spasticity, etc.) that affect the most children?" We have to remember that this statement applies not only to pediatric but general neurosurgery even today. He then added, "Second, the request: will you consider going abroad for a short time to do and teach pediatric neurosurgery in a Third World country?" This is also an important message in functional neurosurgery, as there are enormous needs for functional neurosurgical opportunities in such countries to teach, operate, and learn.

12. Spinal Surgery

The first removal of spinal tumor in the cervical epidural space, believed to be schwanoma, was successfully performed by Dr. Hayashi Miyake, Professor of Surgery at Kyusyu University in 1911. As orthopedic surgery became independent from surgery in 1926, papers on spine were published in both disciplines. In 1948 Japan Neurosurgical Society was founded and spinal papers were also published in neurosurgery journals. Currently there are two spinal societies, Japanese Society of Spinal Surgery (JSSS) composed of neurosurgeons and the Japanese Society for Spinal Surgery and Related Research (JSSR) composed of orthopedic surgeons. Specialty boards of two societies are in preparation to be united in 2017.

Ossification of posterior longitudinal ligament (OPLL), characteristically seen among Asian races, has been intensely studied in Japan as regard to its pathophysiology and surgical treatment(85). In recent years, its genetic analysis is in progress (86).

It is noteworthy that various methods of laminoplasty for cervical spondylotic myelopathy have been proposed in Japan and propagated to the world, as an alternative method to laminectomy (87). iPSCs transplantation therapy will be a promising field in the future (88).

With rapidly progressing aging society as seen in Japan and some other countries, patients' population with spinal diseases especially spodylotic diseases is expected to increase. To cope with this trend, preventive measures and further development of minimally invasive surgery will be necessary.

13. Neurotraumatology

Traumatic brain injury (TBI) stands out as a major health and socioeconomic problem in Japan as in many other countries. During the past 40 years, the treatment of TBI has progressed along with advancing motorization. The main causes for severe TBI used to be vehicle and/or motor cycle accidents. However, due to the rapid increase in aging population, TBI in elderly people occurring in daily life has considerably increased in Japan, prompting a nationwide registration to study on the etiology and pathophysiology of severe TBI.

13.1. The Japan Neurotrauma Data Bank (JNTDB)

The Japan Society of Neurotraumatology (JSNT) has conducted clinical registry, called Japan Neurotrauma Data Bank (JNTDB) projects, three times in 1998, 2004 and 2009, dealing with patients with GCS less than eight and over a period of three years each. In the latest project 2009, a total of 3194 cases were registered from 23 medical centers (89, 90).

13.2. Multimodal Monitoring to Prevent Secondary Brain Injury

Management of severe TBI patients is important to improve the outcome by preventing secondary brain injury. Formerly, ICP (intracranial pressure), CPP (cerebral perfusion pressure), and SjO2 (jugular oxygen saturation) were used in neurointensive care in Japan. ICP monitoring is a "cornerstone" to determine the proper surgical treatment to decrease secondary injury processes, as recommended in the JSNT guideline for the management of severe TBI(91). In addition, cerebral microdialysis has been introduced in Japan since 2004. It serves to estimate neuronal vulnerability, metabolic derangements and vascular autoregulation, providing information as to the outcome and therapeutic planning (92). This monitoring technique has a great advantage for continuous metabolic monitoring at bed side.

14. Future Efforts for Neurotraumain Japan

Rapid expansion of the geriatric TBI (gTBI) population in Japan has caused a significant effect that should not be overlooked (93). Compared to younger TBI patients, gTBIs have a unique pathophysiology (94, 95). It is expected to establish a framework of specific guidelines for the treatment of severe gTBI patients. As a role model of advancing aging society in the world, we should continue to enlighten the public and healthcare professionals regarding primary prevention of geriatric TBIs.

15. Summary

Recent advances in neuroscience across a wide range of disciplines have yet to fulfill their promise in terms of practical applications in neurosurgery. Surgical technologies will need to develop further in an effort to accomplish minimally invasive surgery. Skull base surgery, for instance, is designed to be minimally invasive to the brain, allowing exploitation of the bone to some extent. In the future, however, both brain and bone should be minimally invaded while accomplishing therapeutic goals. To this end, technological developments in other fields like endoscopy and robotics will be helpful.

With the development of basic neuroscience and the accompanying technologies has come the necessity of a renewed scrutiny of indications for surgical treatment. In this respect, so-called translational research will become increasingly important in facilitating the translation of basic sciences to clinical application. Frequently now, clinical trials dealing with big data on various subjects are conducted to determine therapeutic indications for various neurosurgical procedures vis-a-vis non-surgical treatment. This should not be regarded as limiting the territory of surgical treatment, but rather as an invitation to further extend the scope of surgery for the greater benefit of patients. Whatever new surgical fields emerge, the ethical side of treatment should not be forgotten. Robotic surgery should be utilized with the utmost care, as should tissue implantation.

As the late Professor Kenichiro Sugita wrote in his letter to his friends when he published his lifework, the Microneurosurgical Atlas, "The living brain has dignity and beauty. We neurosurgeons are allowed to look at and touch it". "Surgery," he concluded, "like science and art, has no end, and most of it is agony itself." We neurosurgeons operate on the most sublime of all human organs. Even under anesthesia, we know that the brain is living and changing, displaying its multiple facets, as if in a plea to be treated with all due respect. Our efforts to improve neurosurgery should be unceasing.

The next phase in the evolution of neurosurgery will be to evaluate the enormity of the human brain and its power to heal itself. It is now necessary to stop finding ways to reach a target, and to focus rather on changing the target. In essence, tumor surgery is merely a palliative approach that aims to create a space in which, sooner or later, a fresh tumor may occur. The aim of 'curing' should be tempered by that of providing 'relief' from symptoms. After every surgery, the neurosurgeon would do well to recall the words of Ambroise Pare: I made the wound, God healed the wound.

AmbroisePare's book had an influence on surgical practice in Japan in the Edo Era; Seishu Hanaoka performed the first breast cancer surgery under general anesthesia in 1805, preceding Morton's ether anesthesia for thyroid surgery.

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