



## Editorial for Emeritus Professor Yoshikuni Mizuno

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Emeritus Prof. Yoshikuni Mizuno graduated from the University of Tokyo in 1965. He served as Professor of Neurology at the Juntendo University School of Medicine from 1989 to 2006. Dr. Mizuno has published over 600 original articles on Parkinson's disease, related disorders, and others. He is particularly interested in the etiology and pathogenesis of Parkinson's disease. Dr. Mizuno and his collaborators identified the gene parkin for an autosomal recessive form of young onset familial Parkinson's disease. He received many awards for these activities. Dr. Mizuno is an honorary member of the Japanese Neurological Society, a corresponding fellow of the American Neurological Association, an active member of the American Academy of Neurology, and an officer of the Movement Disorders Society from 2005 to 2009 and MDS-AOS secretary from 2005 to 2006. He developed leadership qualities in the international society, such as MDS and MDS-AOS.

Around September 1988, the president and the dean of Juntendo visited him at Jichi Medical University, where he worked. They asked him to succeed Professor Narabayashi, an honorary professor, and take over the neurology course at Juntendo University. At that time, Juntendo University was famous for the neurophysiology. He had been immersed in his work to elucidate the pathomechanisms of Parkinson's disease since he was at Jichi Medical University, and he was worried about whether he could continue that work. However, Professor Narabayashi pioneered stereotaxic surgery, focusing on treating Parkinson's disease, and had many patients. He decided to take up his post at Juntendo University in January of the new year, 1989. The work he was doing at Jichi Medical University was with an animal model caused by MPTP, which was said to be the closest to Parkinson's disease at the time. Somehow, he found that it inhibits complex I of mitochondria, and he thought that the energy

crisis might cause nigral damage in this model. At almost the same time, a group led by Ramsay in the United States was doing the same work, but in an era without email like today, he learned about it later in the literature. The whole brain takes up MPTP. It was known that after being taken up by the brain, MPTP is oxidized to MPP<sup>+</sup> in glial cells by monoamine oxidase and is highly concentrated in nigral neurons. Next is the brain of a patient with Parkinson's disease. Fortunately, he had seven brains that had cooperated in the autopsy and went to Juntendo, but only complex I was reduced in all cases, and complexes II to IV were not reduced. However, it was not clear why the mitochondria were damaged. Then, the story of familial Parkinson's disease came in, and the first to find this was Dr. Matsumine, who was in the department at the time. He found a family linked to a polymorphism in the mitochondria targeting the sequence of Mn-SOD in mitochondria. In a joint study with Niigata University, we found that this family was near the end of the long arm of chromosome 6. In a joint research with Keio University, we discovered the Parkin gene. This is the most common type of recessive inheritance in young-onset recessive families. Later, a group in the UK reported that  $\alpha$ -synuclein accumulates in the nigral mitochondria of Parkinson's disease, and findings linking  $\alpha$ -synuclein and mitochondria were obtained.

On the other hand, in familial Parkinson's disease, regarding the cell degeneration mechanism of Park2, Parkin is a cytoplasmic protein. Still, when damage occurs in the mitochondria, it was found that Parkin gathers around the mitochondria to remove it. In this way, it is becoming clear that the onset mechanism of Parkinson's disease is deeply related to mitochondria. The role of parkin and PINK1, another causative gene for young-onset Parkinson's disease, in mitophagy has thus been clarified. It is well known that inclusion bodies exist in residual cells in many neurodegenerative diseases. Still, it has been revealed that the dysfunction of the protein degradation system induces cell death. This can be said to be a significant discovery.

Dr. Mizuno majored in neurology because he was attracted to the new field of neurology. Another reason

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was that he found the neurological examination procedures interesting, which could be reasoned out. Dr. Mizuno was very attracted to examining a patient's entire body, estimating the location of lesions, and then narrowing down the name of the disease in conjunction with the patient's medical history. When he was a medical student and resident, he often read articles in the *New England Journal of Medicine* in the form of case conferences. There were cases in which a clinical diagnosis of cerebellar hemorrhage was made even though the biopsy was negative and the autopsy confirmed the diagnosis. Also, university conflicts were intensifying when he started working as a doctor. Around the third year after joining the department, he could not continue his training because of these conflicts. He felt he might have to give up his career as a neurologist in Japan, so he decided to go to the United States. Northwestern University, where he studied, is a private medical school in a lovely environment north of downtown Chicago. The neurology department has an excellent teaching system, and he received very fruitful training. He particularly liked the fact that the training system was rotational. Residents spent the first year on the wards, the second year rotated through areas such as neuropathology, EEG, electromyography, and pediatric neurology, and in the third year, after about six months of chief residency, they could choose the area of their choice. His fellow residents were of a high level and had read textbooks and literature very carefully, so they had a great deal of knowledge to base their differential diagnosis on. This environment stimulated him to study as hard as possible to learn as much as possible. His desire to record the vivid impressions he received while studying in the U.S. led to the publication of the "Handbook of Neurology" after returning to Japan and further to the institutionalization of a rotation system of training at Jichi Medical University, which was a newly established medical school. It was his experience as an exchange student in the United States. When he studied in the U.S., treatment with L-dopa had just begun. It was L-dopa alone, without carbidopa or benserazide, as is the case today, but the patients improved remarkably. This was the first time he had seen such improvement in a neurological disease, and his desire to cure patients with his own hands led him to want to specialize in Parkinson's disease. He believes that clinicians, as long as they work at universities, should engage in clinical practice and research from a scientific point of view. The scientific way of thinking cultivated through research is always useful when examining patients. It is important to make a differential diagnosis and select treatment scientifically and logically rather than making a diagnosis based on intuition and experience alone.

Dr. Mizuno has published the "Handbook of Neurology" based on his experiences in the United States. The "Handbook of Neurology" has become an encyclopedia of

the increasingly fragmented field of neurology. "Handbook of Neurology" has included some information on rare syndromes and findings to help residents, graduate students, and young medical advisors in their overall neurological practice. Dr. Mizuno, advocating the necessity of both clinical and research aspects, is highly regarded by people around the world as a top-notch neurologist in both fields. Dr. Mizuno, including Dr. Mochizuki and myself, has nurtured many disciples and has contributed to neurology in Japan and the world.

—The message from Prof. Yoshikuni Mizuno—

It is important to explain to patients what is causing their symptoms. After clarifying the most critical concerns of the patients, we then consider the treatment. It is also necessary for clinical educators to teach this kind of approach to patients. I would also like them to remember to conduct research that will help them develop a scientific perspective. After obtaining a medical specialty, I would like to request that they devote themselves to research for a while and, as a request to their supervisors, divide their time between research and clinical practice to devote their entire energy to both. Neurology is an exciting and profound field in which the traditional clinical approach is still alive. In addition, the differential diagnosis unique to neurology, in which the entire body is examined to determine the etiology, has a wide range of applications. I would be happy if you all take a greater interest in this field.

Here is the biography of Emeritus Professor Yoshikuni Mizuno:

Professor Yoshikuni Mizuno, the second chairperson of the Department of Neurology, Faculty of Medicine.  
Born on February 5, 1941 in Tokyo.

March 1965: Graduated from the Faculty of Medicine, University of Tokyo.

April 1965: Intern at the University of Tokyo Hospital.

April 1966: Internal medicine training at the Third Department of Internal Medicine, University of Tokyo.

May 1966: Passed the 40th National Medical Examination.

April 1967: Joined the Department of Neurology, University of Tokyo.

October 1969: Resident in Neurology, Northwestern University School of Medicine.

September 1973: Lecturer in Neurology, Jichi Medical University.

October 1974: Passed the American Neurological Association specialist examination.

June 1981: Associate Professor of Neurology, Jichi Medical University.

August 1988: Professor in the Department of Neurology, Jichi Medical University.

January 1989: Professor of Neurology, Juntendo University School of Medicine.

March 2006: Retired as Professor of Neurology Juntendo University School of Medicine.

April 2006: Director and Special Professor of the Center for Geriatric Disease Research, Juntendo University (until March 2011).

April 2007: Director of Juntendo Koshigaya Hospital, Juntendo University School of Medicine (until August 2010).

April 2011: Special Professor of Neuroregenerative Medicine, Kitasato University School of Medicine (until August 2013).

2018 to present: Honorary Professor and Visiting Professor, Juntendo University.

**Awards:**

1996: Japan Medical Association Award.

2002: Baelz Award (jointly with Professor Nobutaka Hattori).

2005: Uehara Award.

2007: Purple Ribbon Medal.

2012: Order of the Sacred Treasure, Gold Rays with Neck Ribbon (Jokun).

**Major Society Memberships and Positions Held:**

Movement Disorder Society; Treasurer.

American Neurological Association; Corresponding member.

American Academy of Neurology: Active member.

Japanese Neurological Society; Director.

Japanese Society of Neurotherapeutics; Councilor.

Japanese Autonomic Nervous Society; Director.

Movement Disorder Society Japan; President.

Major Conferences Organized and Participated In:

January 20–21, 1999: Chairperson: The 7th Winter Conference on Neurodegeneration, Karuizawa.

October 4–6, 1999: President; 2nd Asia-Pacific Parkinson's Disease Association International Symposium, Sheraton Hotel, Urayasu.

April 9, 2000: Chairperson: The 2nd World Parkinson's Day. Tokyo.

April 12, 2000: Chairperson; Psychiatric Symptoms of Parkinson's Disease, The 3rd International Congress of Neuropsychiatry Special Symptom 5, Kyoto.

March 31–April 5, 2001: President: The 5th International Conference on Progress in Alzheimer's Disease and Parkinson's Disease. Kyoto.

May 11–14, 2004: President; 45th Annual Meeting of the Japanese Neurological Society, Shinagawa Prince Hotel, Tokyo.

December 2–3, 2004: Chairperson: The 11th Winter Conference on Neurodegeneration, Kyoto.

October 28–November 2, 2006: Chair; Congress Local Organizing Committee; the 10th International Congress of Parkinson's Disease and Movement Disorders (MDS), Kyoto International Conference Hall (KICH), 2006, Kyoto.

October 4–6, 2007: President; 1st Movement Disorder Society, Japan (MDSJ) Academic Meeting, Shinagawa Prince Hotel, Tokyo.

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