The Behind-the-Scenes Story of Developing Aggressive Behavior measurement System（Model ARM-Ⅱ）

About 25 years ago, around 1998, we discovered that mouse offspring exposed to dioxin through the placenta exhibited abnormal aggressive behavior. We named this symptom "Dioxin encephalopathy" and reported it to the Japanese government's Ministry of Health, Labor, and Welfare. In the course of this series of studies, it was necessary to investigate the relationship between the amount of dioxin intake and the intensity of aggression.

At that time, the only available test for assessing aggressive behavior was the Resident-Intruder Test. So, we also conducted this test. It's embarrassing, but we were beginners in behavioral science, so we didn't know about the critical flaws in that method. Remarkably, the Resident-Intruder Test, which was being conducted worldwide, could not measure aggressive behavior in female animals. This was because the Resident-Intruder Test was primarily a testing method for sexually aggressive behavior induced by male hormones.

We searched for an experimental method to measure aggression that occurred purely for psychological reasons, rather than sexual behavior. However, such a behavioral study did not exist. Our response was, "Well, if it doesn't exist, we'll have to create it ourselves!" This was the catalyst for the birth of Aggressive Behavior Measurement System (ARM-Ⅱ). In reality, we were neuroanatomists, so we had limited familiarity with behavioral studies and did not fully understand how challenging it would be to establish a new behavioral paradigm. Young researchers with limited knowledge often make remarkable discoveries, and we felt our situation was somewhat similar.

We had noticed that dioxin encephalopathy mice exhibited a highly aggressive nature, readily attacking experimenters even with slight touches. Laboratory animals are typically bred for docility, and under normal circumstances, they would ignore minor stimuli from experimenters. However, dioxin encephalopathy mice were consistently irritable, easily prone to tantrums and aggressive behaviors in response to minor stimuli. In psychiatric terms, such symptoms of becoming enraged over trivial matters are referred to as "irritability." Just as psychiatric patients sometimes throw fits, lash out at others, or shout loudly over trivial issues, the symptoms of mice with irritability are strikingly similar to those of such psychiatric disorders. Starting from dioxin encephalopathy mice and extending to mouse models of mental disorders, when exposed to anything they can bite, they will attack it indiscriminately. We decided to call this behavior "aggressive biting behavior toward inanimate object: ABI" or "object-directed aggressive behavior". (Please watch the video below featured in the Japanese version, with English subtitles enabled.)

Response to Minor Stimuli: A Comparison between Normal Mouse and Mental Disorder Model Mouse. When touched with a stick, a normal mouse ignores it, while a mental disorder model mouse kicks the stick away with its hind legs or bites it.

Normal mouse.

When lightly tapped on the side with a thin rod inside its home cage, the mouse shows discomfort and moves away, but does not exhibit any further actions."

Mouse model for mental illness.

Similarly, when lightly tapped on the side inside its home cage, the mouse reacts with extreme discomfort, vigorously kicking the rod away with its hind limbs and darting around the cage. When lightly tapped near the head with the rod, it fiercely bites the rod."

We were searching for a method to measure aggressive behavior in mice towards inanimate objects. We arrived at the idea of "lightly touching the mice with a stick to provoke agitation and then moving the stick in front of them to mechanically measure their biting force." We drew a simple design and had the device manufactured by a company specializing in behavioral study equipment. Using this device, we investigated the aggressive biting behavior of animals that had received dioxin through the placenta during the fetal stage. Although this

device was relatively rudimentary compared to the current ARM-II, it allowed us to clearly demonstrate that offspring exposed to dioxin during the fetal stage were more prone to irritability during adolescence and that there were differences in the expression of aggressive behavior between males and females (Kuchiiwa, T. et al., Journal of Kagoshima Junshin Women's University Graduate School Bulletin, 2008).(When viewing the paper, please click on the specific section in the Japanese version.)

The device we created had various performance issues, so we asked a company specializing in the research and development of experimental equipment (Muromachi Kikai Co. Ltd., Tokyo) to improve the device. At that time, Mr. Osamu Murakami, who was the head of development at the company, came to Kagoshima University, and this meeting was not just an initial encounter but rather a "fateful encounter." Mr. Murakami examined the device closely with a stern expression and unexpectedly said, "Let's work together." Instead of just taking an order, Mr. Murakami proposed, "Let's develop a new device together." We were overjoyed that an expert in the development of behavioral testing devices would improve our device free of charge. Thus began the collaborative effort between Mr. Murakami and us, with back-and-forth improvements to the device and behavioral tests using animals conducted in Tokyo and Kagoshima. Development took many years, and in 2011, we obtained a joint patent and launched the product through Muromachi Kikai Co. Ltd. (model ARM-001). ARM's sales did not grow as expected, but it significantly raised ARM's profile globally, and discussions in review articles about psychopharmacology began to suggest that "ARM testing is essential."

However, in August 2020, after Mr. Murakami stepped down as president, Muromachi Kikai Co. Ltd. suddenly informed Kagoshima University and us that they would "discontinue the production and sale of ARM." While we could understand the company's anguish at losing Mr. Murakami, it was truly a bolt from the blue for us, who had spent many years advancing research on the ARM. We consulted with Mr. Murakami (now at the Tokyo Metropolitan Institute of Medical Science) and searched for a company that could take over the manufacturing and sale of ARM on behalf of Muromachi Kikai Co., Ltd. As a result, the following month (September 2020), BioresearchCenter, Inc. (BRC) expressed interest in continuing the development of the successor device, and

the redevelopment of ARM began. However, due to the highly specialized and precise nature of ARM, it was difficult for BRC to construct the technology to detect aggressive biting behaviors, and the redevelopment made slow progress.

Amidst such challenging circumstances, Mr. Murakami graciously offered to recreate ARM, and he proceeded to release the new ARM-II from his newly established company, ExpRessAP. ARM-II is a miraculous device recreated by Mr. Murakami himself who holds the patent rights, and it is truly the embodiment of the "Murakami brand." As co-patent holders, we take great pride in the reborn ARM-II.