

追悼文 名誉会員 故林 裕造 博士

日本毒性病理学会の名誉会員、林 裕造先生におかれましては、平成 29 年 5 月 23 日にご逝去（享年 87 歳）されました。数年来、肝硬変を患い、食道静脈瘤の手術等を受けられていましたが、徐々に衰弱され、とうとう帰らぬ人となられました。心より、お悔やみ申し上げます。



先生の所属した国立医薬品食品衛生研究所は、今年度中に川崎市殿町への移転を予定していますが、林先生は数年前より現所在地の世田谷区上用賀の近くに越してこられたことを知っていました。その当初は、ときどき研究所内でお見かけすることがあり、ぜひ一度ご訪問したいと思っていたところ、果たせずにおわってしまいました。残念で仕方ありません。すぐに面会に行けなかったのは、多少忙しかったせいもありますが、いつも正装して出迎えられると聞いていましたので、こちらも気持ちだけは正装してからと心の準備に手間取ったせいで、折角の好機を失ってしまい、林先生には本当に申し訳ありませんでした。

林先生は、昭和 29 年に東京医科歯科大学を卒業され、昭和 35 年に同大学大学院（病理学専攻）を修了後、塩野義製薬株式会社研究所、米国ウィスコンシン州立大学医学部病理学教室、食品薬品安全センター秦野研究所を経て、昭和 55 年に国立衛生試験所（現国立医薬品食品衛生研究所）の病理部長に着任されました。平成 3 年に、小生の現職である安全性生物試験研究センター長に就任され、平成 7 年に定年退官されました。林先生は、医薬品、食品関連物質、環境化学物質全般にわたるリスクアセスメントを推進され、国立医薬品食品衛生研究所の掲げるレギュラトリーサイエンスの開拓者のお一人と言っても過言ではありません。そのお考えは、林先生よりサイン入りでいただいた書籍『毒性学ノート・化学物質との共存』に凝縮されています。ご定年 6 年後の平成 13 年の暮れに刊行されていますが、残念ながら非売品なので、一般には入手が難しいかもしれません。16 年前の書籍でありながら、現在にも十分通用する内容です。たとえば、今後の展開として、動物愛護に伴う既存の動物試験の削減の方向とその反対軸となる先端技術を応用した新規の試験法開発の方向をすでに予見されていました。現在注目されている *in silico* 法や toxicogenomics/pharmacogenomics の導入についても言及されています。

いつも理詰めのお話で、付け入るスキがほとんどなかったのですが、時には真顔で冗談を言われることもありました。よく知られているのが、リスクアセスメントに対する大きな 2 つの誤りとして、1 つは高度先端技術の裏付けがあることによる「魔法の弾丸」と受け止める誤解、もう一つは「リクツアワズメント」すなわち「理屈合わすメント」と帳尻合わせと見立てる誤解であると、『毒性学ノート』にも記述されています。実際の業務に携わっている当事者として、言い得て妙とはこのことと納得しています。林先生のご高名は、以前より存じていましたが、特に鮮明な出来事は私の恩師かつ先輩である森 秀樹先生との邂逅にまつわるエピソードです。林先生のお言葉をそのままお借りすると、「君の先輩の森 秀樹君は相当変わっているね。突然部屋に入ってきて、ぶっきらぼうに書類に印鑑を押してほしいと言う。よく聞いてみると、教授選の推薦状のこのようでした。」。多少の脚色はお許しいただきたいが、内容については当の森先生も強く否定されないところをみると、概ね真実に近いものと信じています。「秀でている」を「変わっている」と表現されているのだと直感しました。森先生が岐阜大学学長まで務められたことは、皆さんご存知のことと思います。ちなみに、当

時米国留学中であった小生が国立衛生試験所に赴任することになったのは森先生の推薦によるものです。

林先生は、国内外の委員会等でもリーダーシップを発揮されました。特に、医薬品規制調和国际会議（ICH）とFAO/WHO食品添加物専門家会議（JECFA）ではお世話になりました。ICHでは、ICH発足当初のがん原性試験に関する会議に呼び出され、何のことかわからないままに終了しましたが、どうも勝手に座った席が座長席の隣だったようです。こぶる居心地が悪く、よく事情を訊いておけばよかったと猛省しきりだったことを憶えています。また、JECFAは林先生が務められていた参与を小生が直接引き継ぎました。引き継いだ当初のことですが、カナダの女性がドキュメントの書き方を林先生から直接指導されたと真顔で話していました。小生には今でもとてもできないことです。

林先生の研究のご業績は、退官記念講演会で拝聴することができました。この講演会を企画したのが小生であったことから、『毒性学ノート』でも、「業務の引き継ぎと資料の整理に明け暮れていたある日、病理部第2室の西川秋佳博士から退官記念講演会を予定しているとの申し出があり」との記載があり、今でも恐縮しています。ちなみに、小生はずっと病理部第1室の所属であり、さすがの林先生もうっかり記憶違いをされたのかと思っていたところ、当初は第2室に所属し、その後第1室に配置換えになったことを思い出しました。かように、林先生の記憶力はすべてにおいて正確無比でした。研究の内容については、4-ニトロキノリン 1-オキシド（4-NQO）関連物質の発がんメカニズムを電子顕微鏡、ポストラベル法を含めて包括的に解析され、その全容解明の一端を担われました。発がん性以外にも、化学物質による肺高血圧症、脂質症、肝内胆汁うっ滞などの発症メカニズムについても綿密に解析され、毒性病理学の発展に大きく寄与されました。

ご息がいなかったこともあり、林先生と懇意にしていた小生の友人が遺品整理をしていたところ、お亡くなりになる1ヵ月前にも食品関連物質の安全確保に関する多くのメモ書きが残されていたようです。我々の至らなさに、つくづく歯がゆい思いをされていたものと申しわけなく思いますが、後は何とかなりますので、どうか安らかにお休みください。ご指導いただき、本当にありがとうございました。

2017年6月27日

国立医薬品食品衛生研究所

安全性生物試験研究センター長

西川 秋佳

In Memoriam:

Honorary Member, Yuzo Hayashi, M.D., Ph.D., 1930-2017

Dr. Yuzo Hayashi, Honorary Member of the Japanese Society of Toxicologic Pathology, passed away on May 23, 2017, at the age of 87. He was suffering from liver cirrhosis for the last several years. He also had surgeries with esophageal varix and received other treatment, gradually weakened, and deceased without regaining his health. I would like to express my sincere condolence.

The National Institute of Health Sciences (NIHS) which Dr. Hayashi used to belong to, is to be relocated to Tonomachi, Kawasaki, before the end of the Fiscal Year 2017. Dr. Hayashi moved to the residential area near NIHS at the current location in Kamiyoga, Setagaya-ku, several years ago. Soon after his relocation, I saw him occasionally within NIHS. I wanted very much to visit him at his new home, but could not make it, which I truly regret. I was a little too busy to visit him, but the real reason why I could not make it was that it took me too long to be ready for my meeting with him since I heard that he would always dress formally to welcome his visitors, and I wanted to be worthy of his formal welcome at least in my heart. I feel it very sorry to Dr. Hayashi for that I missed the best opportunity to spend time with him.



Dr. Hayashi graduated Tokyo Medical and Dental University (TMDU) in 1954, and joined the research institute of Shionogi and Co., Ltd., in 1960 after completing his graduate study at TMDU (majored in Pathology). In 1980, he assumed the position of Director Pathology Division of National Institute of Hygienic Sciences (the current NIHS), after having engaged in his research activities at Pathology Division, Medical School, Wisconsin State University in the United States, and Hatano Research Institute of Food and Drug Safety Center in Japan. In 1991, he was promoted to the Director of Biological Safety Research Center of NIHS (my current position), and took mandatory retirement in 1995.

Dr. Hayashi promoted the concept of risk assessment in drugs, food related substances, environmental chemicals, and etc., and it is no exaggeration to say that he was one of the key pioneers of regulatory science that has been advocated by NIHS. His philosophy of risk assessment is compiled and condensed in his book, "Toxicology Notebook: Co-existence with Chemical Substances" (in Japanese), which he kindly gave me with his signature. The book was published in 2001, six years after his retirement. Unfortunately, the book is not for sale, and it is difficult to obtain for general readers. The contents are still current and valid though it was published 16 years ago. In his book, Dr. Hayashi predicted the current trends of reducing the traditional animal testing with consideration to animal welfare, and in parallel developing new test methods with application of the state-of-art technologies. He referred to the application of in silico methods, toxicogenomics/pharmacogenomics, and others as well.

Dr. Hayashi's talk was always logical and reasoned, and we could hardly make any arguments.

However, he sometimes made a joke with a straight face. His famous jokes related to the two big misunderstandings of risk assessment: the first one is assuming risk assessment as a “magic bullet” with supportive evidences of the state-of-art technologies; and the other is assuming risk assessment as something to manipulate accounts, ; he said “rikutsu awasumento” in Japanese, meaning coming up with a convenient and plausible story. These two big misunderstandings of risk assessment were described in his book, Toxicology Notebook, mentioned earlier. As a scientist practicing risk assessment, I am truly convinced that the way Dr. Hayashi described risk assessment was perfect.

I had long known Dr. Hayashi by reputation, and the most unforgettable episode with him was a story that he told me about his encounter with Dr. Hideki Mori who was my mentor and senior researcher at Gifu University. With the exact words by Dr. Hayashi, “Dr. Hideki Mori, who is your senior at Gifu University is an eccentric person. He abruptly came into my room and asked me to give a seal on a document. I asked him what the document was for and found that it was a recommendation letter for him to apply a professor position of Gifu University.” This may embrace some dramatization by me, but Prof. Mori himself did not strongly deny the story, and thus I believe this was what happened between them. I understood intuitively that Dr. Hayashi was trying to express the brilliant of Dr. Mori by saying “eccentric.” It is also known that Dr. Mori served as President of Gifu University. While I was engaged in my research in the United State, Dr. Mori recommended me for a position at NIHS.

Dr. Hayashi demonstrated excellent leadership in committees within Japan and globally. Especially, I owe him very much in the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the Joint FAO/WHO Expert Committee for Food Additives (JECFA). At ICH, I was summoned to the meeting to discuss carcinogenicity studies organized soon after ICH was established, but the meeting ended before I could understand the ongoing discussions. I happened to sit next to the chairperson and was quite uncomfortable during the meeting. I remember regretting a lot wishing that I could have asked Dr. Hayashi about the meeting beforehand. At JECFA, I succeeded to the position of councilor from Dr. Hayashi. Soon after I assumed the position, a representative from Canada told me that she learned from Dr. Hayashi how to prepare the documents. Something I can hardly offer even now.

I learned the research achievements of Dr. Hayashi in his lecture given at the time when he retired from NIHS. I organized a lecture meeting outside NIHS, which was described in his book, Toxicology Notebook: “While I was busy handing down my duties to the successor and organizing the related materials, Dr. Akiyoshi Nishikawa of 2nd Section of Pathology Division told me that he was planning a lecture meeting for my retirement”. I am still very thankful to him for mentioning my name in his book. By the way, I was believing that I belonged to the 1st Section of Pathology Division since I started at NIHS, and thought that even Dr. Hayashi made a mistake in his memory. But I realized later that I started at the 2nd Section first and relocated to the 1st Section in NIHS. Dr. Hayashi’s memory always had unmatched accuracy. His achievements include comprehensive analyses of the carcinogenicity mechanisms of 4-nitroquinoline-1-oxide (4-NQO) using the methods including electron microscope and post-labeling, which contributed to elucidate its whole mechanisms. In addition to his studies in

carcinogenicity, Dr. Hayashi conducted detailed analyses of the mechanisms of pulmonary hypertension, lipidosiis, intrahepatic cholestasis, and etc., developed by chemical substances, which contributed to the advancement of toxicologic pathology.

As Dr. Hayashi had no children, one of my friends who was close to him was sorting through his possessions after his death, and he found numerous notes on how to assure safety of food-related chemical substances, written by Dr. Hayashi only about one month before his death. He must have been really frustrated with the incompetency of those who succeeded him including myself. May his soul rest in peace. We would do our best to succeed his wishes. Lastly, I would like to express my wholehearted gratitude to Dr. Hayashi for his guidance and support.

June 27, 2017

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