

MY WARM MEMORIES OF JAMES R. GILLETTE

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It is a great pleasure to present my appreciation and memories of Dr. James R. Gillette at the National Institutes of Health (NIH, Bethesda, MD). In 1957, I engaged in the study of the metabolism of serotonin and catecholamine as a neuropsychiatrist at the Institute of Pharmacology, University of Milano, Italy. I met with Dr. B. B. Brodie, Chief, Laboratory of Chemical Pharmacology, National Heart Institute, NIH, in Milan, and he kindly invited me to his laboratory to study serotonin and catecholamine metabolism.

In fall 1958, during my studies of serotonin metabolism, I found by chance that the administration of chlorpromazine induced hepatic metabolism of pentobarbital. After that, I intensively engaged in studies on drug metabolism, especially the induction and inhibition, developmental and aging aspects, and sex-dependent differences of hepatic microsomal drug-metabolizing enzymes.

Throughout these studies, I realized that the field of drug metabolism research would become an important field of the medical sciences. I subsequently decided to continue my research on drug metabolism in Dr. B. B. Brodie's laboratory in Bethesda, which was a mecca of drug metabolism research at that time and where Drs. J. R. Gillette, A. H. Conney, and J. J. Burns were working. At the end of August 1962, I left Milan and joined the Laboratory of Chemical Pharmacology at NIH in Bethesda to work with Jim Gillette. At that time, I was 32 years old and Jim was 35 years old.

My impression of Jim was of a pure and fervent scientist, and he was writing and correcting papers for his ideas everyday with his characteristic left-handed manner. Since I was an established scientist in the field of drug metabolism study, Jim kindly suggested to me "Ryuichi, you can do your research as you like by continuing your research in Milano." Therefore, I began my research on the effects of some nonphysiological and pathological conditions in the regulation of hepatic microsomal drug-metabolizing enzymes (MDME) using male and female rats.

We found that starvation, adrenalectomy, hyperthyroidism, alloxan diabetes, morphine treatment, and formalin administration all decreased activity of MDME, such as hexobarbital hydroxylation and aminopyrine *N*-demethylation in male rats, except for the sex-related metabolic enzyme activities, such as aniline hydroxylation. Under these conditions, the MDME activities were not decreased in the tissues of female rats. We concluded that MDME activity, which is induced by androgens, is easily ameliorated under pathological conditions; however, the basal enzyme activity in female rats was not affected by such pathological conditions. At this time, the role of cytochrome P450 in MDME was not established, and it was generally considered that only one MDME existed in rat liver microsomal fraction. Therefore, our results received considerable attention, and two articles published in the *Journal of Pharmacology and Experimental Therapeutics* have been cited by many investigators (Kato and Gillette, 1965a,b). One article by Kato and Gillette (1965b) was cited more than 1000 times and was considered in *Current Contents* as

"This Week's Citation Classic" in 1986. The other article (Kato and Gillette, 1965a) was cited more than 800 times. A few years later, Jim told me "Ryuichi, your two papers on the work performed at NIH are the best cited paper in my list of publications."

He liked theoretical matters, and later in his career, he was enthusiastic in establishing new mathematical models for pharmacokinetics and toxicokinetics, accounting for his prolific vitae in the last 15 years of his career.

One thing I have deeply regretted, together with Jim, was the fact that we could not publish a critical paper on the induction of cytochrome P450 by phenobarbital. During the time in Bethesda with Jim, I found that feeding rats with sucrose resulted in a rapid decrease in the hepatic MDME activities and a pronounced change in the color of the microsomal fractions from rat liver (i.e., changed from reddish-brown to white), whereas in contrast, phenobarbital treatment resulted in the color of the liver fractions becoming deep red. At that time, the preliminary paper by Omura and Sato had just been published, and we realized from their results that phenobarbital most likely induced microsomal P450. We initiated studies to confirm this possibility, but unfortunately, the one dual-wave spectrophotometer at the Laboratory of Chemical Pharmacology was broken, and therefore we could not complete these studies.

A portion of our preliminary data was reported at the Federation Meeting in April 1964. During the preparation of a manuscript on our results, Dr. Sten Orrenius' article was published in *Biochemical and Biophysical Research Communications* in June 1964 (Orrenius and Ernster, 1964), and our exciting publication was no longer seminal for the field.

Dr. James Gillette was a fervent, kind, and warm scientist with splendid ideas, and he taught me many things during my 2-year stay in Bethesda.

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Ryuichi Kato was born in 1930 in Hokkaido, Japan. He received his medical degree in 1954 from the Keio University School of Medicine. In 1957, he was a Visiting Fellow at the Institute of Pharmacology, University of Milan, Italy, and in 1962, a Visiting Scientist at the Laboratory of Chemical Pharmacology, NHI, National Institutes of Health, Bethesda, MD. In 1964, he became Section Chief of the Department of Pharma-



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cology at the National Institute of Hygienic Sciences in Tokyo. In 1970, he became Director of the Biological Laboratory, Central Research Institute, Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan. Beginning in 1977, Dr. Kato served as Professor of Pharmacology at the School of Medicine, Keio University, Tokyo, and became Emeritus Professor in 1995. Awards and appointments: academic award, Princess Takamatsu Cancer Research Foundation

(1982); medical award (Basic Medicine), Japanese Medical Association (1992); academic award, Japanese Society for the Study of Xenobiotics (1994); society award, Pharmaceutical Society of Japan (1995); President of the International Society for the Study of Xenobiotics (1987–1988); President of the Japanese Pharmacological Society (1993); President of Japanese Society for Clinical Pharmacology (1995).