

I am deeply indebted to the Japan Endocrine Society

Yutaka Oki *Honorary Member, The Japan Endocrine Society**Academic Consultant & Director, Center of Diabetes and Endocrinology, Hamamatsu-kita Hospital, Hamamatsu, Japan*

Celebrating the 100th Anniversary of the Japan Endocrine Society

It is my heartfelt pleasure to celebrate the 100th anniversary of the Japan Endocrine Society (JES). Writing this essay has brought back many memories from my student days. The first lecture on endocrinology I attended was on November 7th, during my third year of medical school. Prof. Teruya Yoshimi (Fig. 1) delivered the lecture, which focused on the circadian rhythm of cortisol. This intriguing topic marked the beginning of my journey in researching the hypothalamic-pituitary-adrenal axis, which continues to this day. I became a member of the JES the month after I graduated from medical school, even before receiving the results of the medical licensing examination. I think such early membership was uncommon at the time. However, I believe my decision was the right one, as I have enjoyed endocrinology throughout my career.

A Patient

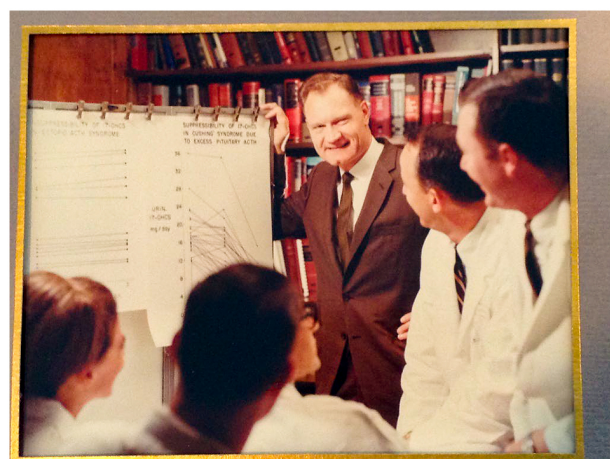
During my second year as a physician, I vividly remember a patient I encountered. She was a young woman in her twenties with typical symptoms of Cushing's syndrome, including central obesity and moon face, accompanied by hypercortisolemia. At that time,

**Fig. 1** Prof. Yoshimi

ACTH measurements were considered unreliable, but at least its suppression was not observed. A dexamethasone suppression test using Liddle's method suggested Cushing's disease. MRI was not available at that time, and CT scans did not reveal an adrenal tumor. A CT scan of the pituitary also failed to detect a tumor. We proceeded with pituitary surgery, but unfortunately, it was unsuccessful. Without access to metyrapone, we tried bromocriptine and other treatments, but she passed away. Since then, I have taken a keen interest in Cushing's disease and have come to deeply admire Prof. Grant W. Liddle (Fig. 2), who developed the dexamethasone suppression test. In graduate school, I worked on producing antibodies against ACTH and vasopressin while establishing radioimmunoassay techniques. I am deeply grateful to my mentors who laid the foundation for me: Doctors Hiroyuki Kurahachi, Masataka Nanno, Shozo Ohgo, and Issei Tanaka.

Grant Liddle Society

After completing my graduate studies, I had the opportunity to work as a researcher at Vanderbilt University in the laboratory established by Prof. Liddle.

**Fig. 2** Prof. Liddle

Although Prof. Liddle had already retired due to a stroke, I was fortunate enough to meet him in person. Under the supervision of Prof. David N. Orth (Fig. 3), who succeeded Prof. Liddle, I conducted research on ACTH secretion. Prof. Orth was exceptionally intelligent and had a significant impact on my research on the pituitary gland. During my final year of study abroad, Prof. Liddle passed away from leukemia. I still remember the profound silence that enveloped Vanderbilt University on the day of his death. The laboratory continues its legacy to this day, and its former members hold an annual reunion as the Grant Liddle Society. Prof. Lewis S. Blevins, formerly the director of the Pituitary Center at Vanderbilt, published a book titled *Cushing's Syndrome*, in which I also contributed as a co-author. Mr. Alexander Faje, who was a medical student at Vanderbilt University, became interested in Japan after reading that book. He visited Hamamatsu and stayed for 10 months. Mr. Faje has had a great career and is now a staff physician in the Neuroendocrine Unit at Massachusetts General Hospital.

Friendships

After returning to Japan, I was encouraged by Prof. Yoshimi and Prof. Hirotohi Nakamura to continue my research on pituitary and adrenal diseases, which I was able to pursue until my retirement. I fondly remember the days spent honing my skills alongside many colleagues, especially Drs. Hiroshi Morita and Kazumi Iino. During this time, I learned from the great works of pioneers in the field, such as Professors Kozo Hashimoto, Yukio Hirata, and Toshihiro Suda. Their passion and knowledge in endocrinology were truly remarkable.

Thanks to my involvement in the JES, I have been fortunate to build many enduring friendships. In particular, I received valuable guidance from Prof. Yasumasa Iwasaki, who belongs to the same generation, and Dr. Kazunori Kageyama, one of my junior colleagues.

In pituitary clinical practice, collaborating with neuro-

surgeons who possess outstanding skills in pituitary surgery has been essential, and Dr. Shigeru Nishizawa and Dr. Shozo Yamada have successfully operated on many difficult cases.

Establishing Radioimmunoassays

When I began my basic research, various hormone radioimmunoassays (RIA) had already been established and reported. However, very few RIAs were capable of measuring hormones at extremely low concentrations, such as ACTH and vasopressin. Much of the research I conducted in graduate school involved creating hormone-specific antibodies. I spent countless days injecting New Zealand rabbits weekly, collecting blood samples from their ears, and measuring antibody titers. The first antibody I successfully created was against AVP, but the iodination and purification of AVP proved particularly challenging. Due to its ring structure, reducing agents could not be used, and purification required ion exchange chromatography. I struggled with the chemistry involved, so I studied diligently every day. After successfully creating the AVP antibody, I was able to produce antibodies for ACTH as well. Measuring these hormones in biological samples for the first time was deeply moving. At that time, there was speculation that AVP might function as a corticotropin-releasing factor (CRF), which motivated me to dedicate myself to establishing AVP-RIA. However, Prof. Wylie Vale later discovered CRF from sheep brains. Nonetheless, I earned my degree through research using AVP-RIA. Subsequently, I created antibodies against CRF, GHRH, CCK8, and Angiotensin II, among others. I described these achievements in my application for a research position abroad, which likely caught my mentor's attention. During my study abroad, Prof. Orth, renowned for having established the world's most sensitive ACTH-RIA at that time, became my mentor. While modern research is conducted using advanced techniques, these advancements remind me of the steady efforts required in the past.

Microperfusion

At Prof. Orth's laboratory, I conducted research using the rat pituitary cell microperfusion method established by Dr. Toru Watanabe to study the kinetics of ACTH secretion. This method involved packing pituitary cells with Sephadex G10 into an extremely small 50- μ L glass column, using a sophisticated pump circulating the culture medium. The setup was placed in a large 37°C room where I worked, collecting samples every 30 seconds to a minute. I carefully handled the samples to avoid spilling,

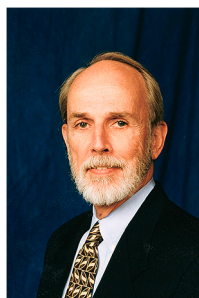


Fig. 3 Prof. Orth

while observing the droplets of culture fluid. We measured the ACTH levels in 4,000 to 5,000 ACTH samples per week using the world's most sensitive RIA. To this day, I have not encountered another method capable of such detailed research on pituitary hormones. Using this system, we demonstrated that the cAMP and inositol trisphosphate/diacylglycerol/protein kinase C pathways play crucial roles in ACTH secretion. At the time, Prof. Yasutomi Nishizuka's articles on protein kinase C, particularly those published in *Nature* and *Science*, served as invaluable references. Like many Japanese fellows, I conducted research late into the night, and my supervisor generously arranged for me to work with an assistant. Her name was Hope, an elderly woman who kindly measured hormones for me. Subsequently, members of my research group continued their studies and obtained many research results on the intracellular signaling system involved in ACTH secretion (Fig. 4).

Clinical Work in Pituitary and Adrenal Diseases

As I mentioned earlier, my interest in pituitary and adrenal endocrinology began with a patient with Cushing's disease. However, due to the rarity of Cushing's disease, I encountered more patients with hypopituitarism or acromegaly in actual clinical practice. There is a famous phrase, "Patients are the textbooks,"

and it holds true. Early in my endocrinology practice, I saw a patient with Sheehan's syndrome who had remained undiagnosed for an extended period. She was entirely inactive and barely spoke. When I began treatment with 20 mg/day of hydrocortisone, she was running around the ward and in a manic state the following day. This experience taught me the importance of starting with a low dose of glucocorticoids in patients who have been in adrenal insufficiency for a prolonged period. At that time, I created a handmade adrenal insufficiency card, which has since evolved into patient-carried and medical emergency cards (Fig. 5). In acromegaly patients, I discovered a clinical sign where, when making a fist, the nails do not get hidden by the palm (Fig. 6). Naming it the "fist test," I was delighted to see it gain widespread recognition among many physicians. These experiences remind me of how much I have learned from my patients.

It is deeply moving to reflect on how I have remained captivated by endocrinology since my initial encounter at the age of 21. Even now, as I continue clinical work in pituitary and adrenal diseases, I have opportunities to discuss cases with younger generations during ward rounds, which keeps me feeling youthful.

I believe that many members share the same sentiments, and I wish for the continued development of the JES, which has brought so much joy to my life.

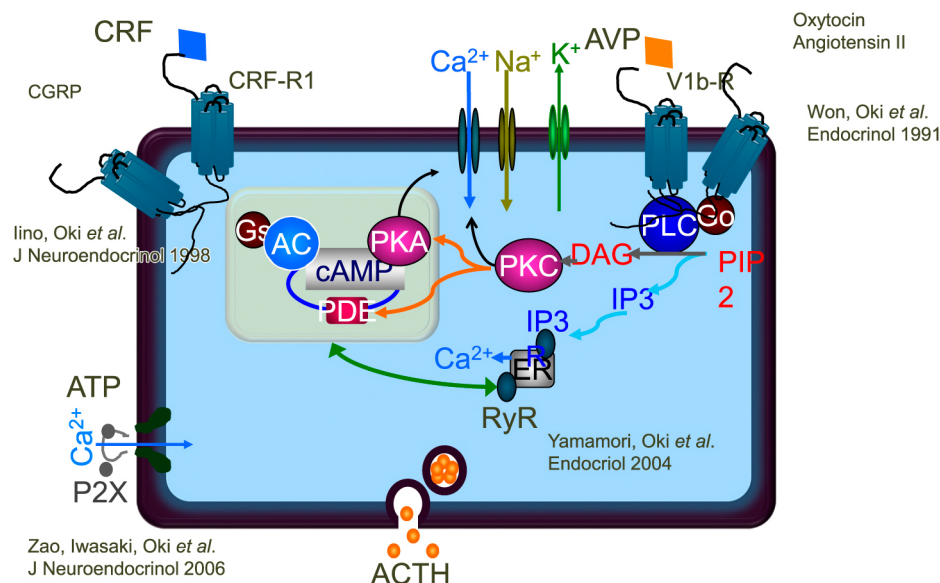
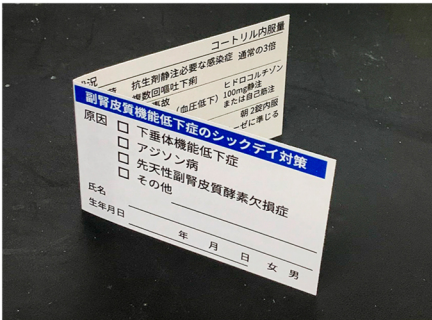


Fig. 4 Signal Transduction mediating ACTH secretion



普段から気をつけましょう		副腎皮質機能低下症のシックデイ対策	
1. 薬は忘れずに指示通り内服する 2. 規則正しい生活を心掛ける 3. 睡眠時間を十分とる 4. 手洗いうがいをして風邪を予防 5. 食事のバランスに気をつける 6. 気分転換や運動を心がける 7. 太りにすぎに注意		原因 ☐ 下垂体機能低下症 ☐ アジソン病 ☐ 先天性副腎皮質酵素欠損症 ☐ その他	
氏名 _____		生年月日 _____ 年 月 日 女 男	

状況		コートリル内服量		状況		コートリル内服量	
発熱	>37.5℃	通常の2倍	重度負荷	抗生剤静注必要な感染症	通常の3倍	複数回嘔吐下痢	通常の3倍
	>38.5℃	通常の3倍					
	>39.5℃	通常の4倍	超重度負荷	重大事故	ヒドロコルチゾン		
軽度負荷	低気温（冬期室外）	通常の1.5倍		ショック（血圧低下）	100mg静注		
	軽度身体負荷			意識消失	または自己筋注		
中程度負荷	抗生剤内服必要な感染症	通常の2倍	手術	外来手術	朝2錠内服		
	単回の嘔吐・下痢		通常手術	通常手術	副腎クリアーゼに準じる		
	強度身体負荷（登山）						

緊急時連絡先

救急車（119）

緊急時のお願い

救急担当の先生にお願い

私は、副腎皮質機能低下症のため、ステロイドの補充治療中です。もし、私が倒れたり、ぐったりしている時は、医療機関で、緊急処置が必要な状態です。救急車（119）を呼んで下さい。裏面に詳細

私は、下記の疾患です

☐ 下垂体機能低下症 ☐ アジソン病

☐ 先天性副腎皮質酵素欠損症

☐ クッシング症候群術後（下垂体 副腎）

私の現在の治療内容

薬品名（ ）

1日（ ）mg 朝（ ）昼（ ）タ（ ）

シックデイには2～3倍内服するよう言われています

他の補充療法 ☐ 甲状腺ホルモン ☐ 性ホルモン

☐ 成長ホルモン ☐ デスモプレシン

私の名前 _____

住所 _____

電話番号 _____

緊急連絡先（続柄） _____

浜松北病院 代謝・内分泌 053-435-1111

担当医 _____

Fig. 5 Emergency card for Adrenal insufficiency (In Japanese)



Fig. 6 Fist test "Positive"



Yutaka Oki

Honorary Member

Academic Consultant & Director, Center of Diabetes and Endocrinology, Hamamatsu-kita Hospital

E-mail: okitaka@td5.so-net.ne.jp

Careers in JES

2024– Honorary Member

2021– Senior Councilor

2017–2021 Director (Education and Career Development)

2015–2018 President, Tokai Regional Branch

1990– Councilor

1980– Member

Activities in JES

2016 Chair, 16th Annual Meeting of JES Tokai Regional Branch

JES Awards

2020 Distinguished Endocrinologist Award

Contributions to EJ

2009– Editor