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JA SYMPOSIUM

Outstanding circulation research by Japanese scientists

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To begin the symposium, I would like to provide an overview of some of the outstanding research conducted by Japanese scientists. Most of these scientists have produced innovative chemical or pharmaceutical inventions, reflecting the Japanese cultural characteristic of "Japanese craftsmanship."

Isolation of ephedrine by Nagayoshi Nagai

Ephedrine is an active constituent of traditional Chinese medicines found in the herb má huáng (*Ephedra sinica*). Among anesthesiologists, this medicine is well known as a sympathomimetic amine commonly used to treat the hypotension associated with nerve blocks and anesthesia. Doctors in the field of internal medicine variably categorize ephedrine as a bronchodilator, decongestant, or appetite suppressant. Nagayoshi Nagai first isolated ephedrine from *Ephedra vulgaris* in 1885. Nagai recognized ephedrine as being the active component of the plant. Although Nagai himself did not study the biological action of this substance in detail, his followers completed the synthesis and structural elucidation of ephedrine in 1929 [1].

Nagai was born in Tokushima Prefecture as the son of a traditional medical doctor. He had the opportunity to learn about Western medicine (known in Japanese as *rangaku*) at the German Medical School of Nagasaki (Igaku-Denshusho) in 1864. Amidst the drastic cultural changes of the early Meiji-era, Nagai continued his studies at Tokyo Imperial University. He became the first doctor of pharmacy in Japan and was sent to the University of Berlin under government sponsorship. In Berlin, he completed a doctorate in 1873 with a study on eugenol, while working as an assistant in August Wilhelm von Hofmann's laboratory. Nagai returned to Japan in 1883 and obtained a position at Tokyo Imperial University, where he became a Professor of Chemistry and Pharmacy in 1893. After the isolation of ephedrine, his research focused on the chemical extraction and analysis of various Japanese and Chinese traditional herbal medicines [2].

Nagai established the Pharmaceutical Society of Japan (PSJ) and became its first president. In honor of his achievements and contributions to Japanese Chemistry and Pharmaceutical Science, he is still known as the "father" of this field. Statues of Nagai can be seen in the entrance hall of the PSJ office building and at Tokushima University (Fig. 1). His name is still on the label on the ampoules of ephedrine to commemorate his name.

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Fig. 1 Statue of Nagayoshi Nagai at Tokushima University

Isolation of adrenaline by Jokichi Takamine

Adrenaline (also known as epinephrine) is a hormone and neurotransmitter that increases heart rate, constricts blood vessels, and dilates air passages. It is the main activator of the sympathetic nervous system. Chemically, adrenaline is a catecholamine, a monoamine produced only by the adrenal glands from the amino acids phenylalanine and tyrosine. Jokichi Takamine named the substance adrenaline and filed a patent application for his discovery on November 5, 1900. Thomas Aldrich published the correct chemical structure, and Parke-Davis began marketing the product under the trade name Adrenalin.

Takamine was born in 1854 in the small town of Takaoka in Japan. At the age of 12, he began to study "foreign science" in Nagasaki, and at the age of 24, he was sent by the government to study technology at the University of Glasgow. Takamine first worked in Chicago and then in Peoria, Illinois, applying the Japanese *sake*-making process to the beer and whiskey industry by substituting the fungal starch-digestive enzyme with malt. Distressed by a mysterious fire in his laboratory and a conflict with local distillery manufacturers, however, he was forced to give up his fermentation business.

Takamine isolated the yeast enzyme diastase, and in 1894 he was granted a patent titled "Process of Making Diastatic Enzyme" (US Patent 525,823), the first patent on a microbial enzyme in the United States. He licensed diastase to Parke-Davis of Detroit under the brand name Taka-diastase. The product sold extremely well worldwide, and Takamine became a big success in the pharmaceutical industry.

In 1895, George Oliver and Edward Schäfer discovered that when adrenal gland secretions were injected into

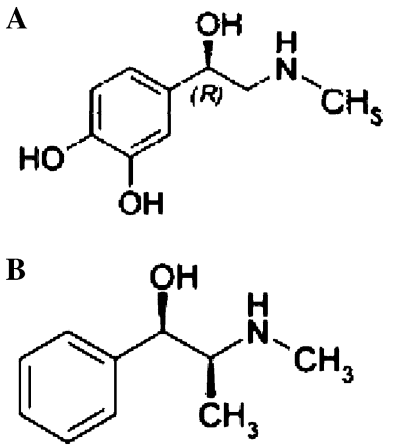

Fig. 2 Structural similarity in the chemical formulae of adrenaline (**a**) and ephedrine (**b**)

experimental animals, the animals' blood pressure increased. Parke-Davis encouraged Takamine to work on the isolation and purification of this vasoactive substance from the adrenal gland. The purification of the substance became a matter of great interest. In 1897, John Jacob Abel in the United States, Furth in Germany, and Schafer and Moore in Britain all aimed to be the first to crystallize the substance. Abel thought that he had succeeded when he obtained a crystalline active and named it epinephrine. (It was later shown that Abel had isolated a benzoyl derivative rather than the pure adrenaline.) Meanwhile, using the profits from Taka-diastase, Takamine hired a young chemist from Japan, Keizo Uenaka, to assist him. Uenaka moved to the United States after completing his education in chemistry under Nagayoshi Nagai. With the help of Uenaka's logical perspective and careful experiments, Takamine successfully isolated and purified the active substance from the adrenal gland in June 1900 [3] (Fig. 2).

The use of adrenaline rapidly became widespread in surgery, where it was used to control hemorrhage. Adrenaline was also applied in cardiology, obstetrics, and the treatment of asthma and other allergies. The discovery of adrenaline enjoyed medical and popular attention: a well-known champion boxer always kept adrenaline on hand when he went into the ring to treat minor bleeding and swelling after being punched.

After Takamine's death (1922), controversy emerged over who was actually the first to purify adrenaline. John Jacob Abel persisted in the belief that he was the first and that Takamine's product was not pure. Almost 100 years after Takamine and Uenaka isolated adrenaline, the debate was settled and Takamine's and Uenaka's claim was confirmed [4]. Adrenaline was first synthesized in the laboratory by Friedrich Stolz and Henry Drysdale Dakin, each working independently, in 1904, which further expanded its market.

Takamine used the royalties from Adrenalin and Takadiastase to enlarge his pharmaceutical business. Together with Matasaku Shiobara, he expanded the pharmaceutical company Sankyo Inc. in Tokyo in 1913. In his later life, Takamine made efforts to improve the position of Japanese immigrants in the United States. He was a key person in the newly founded "Nippon Club," a Japanese Society in the United States. He also tried to foster better relationships between Americans and Japanese. In 1909, Takamine funded a gift of 2,000 cherry trees to the city of Washington, D.C., to decorate the Tidal Basin area around the Potomac River. This symbol of Japanese–American friendship has become a tourist attraction.

Discovery of Kawasaki disease by Tomisaku Kawasaki

Kawasaki disease (KD), also known as Kawasaki syndrome, is an autoimmune disease characterized by inflammation of the medium-sized blood vessels all over the body. Most patients are children under 5 years of age. KD affects many organs, particularly blood vessels, skin, mucous membranes, and lymph nodes. The most serious effects are observed in the heart, where it can cause fatal coronary artery aneurysms if left untreated. When KD is inappropriately treated, mortality is reported to approach 1%. The pathogenesis of KD is suspected to precede viral infection.

Kawasaki disease is named after Japanese pediatrician Tomisaku Kawasaki (born in 1925), a graduate of Chiba University, who was the first to observe the condition in 1961. He published details of the symptoms of the disease, including erythematous skin, conjunctivae and oral mucosa, edema of the hands and feet, cervical lymph node enlargement, and intermittent high-grade fever, often up to 40°C, in the acute phase of the disease in Japanese in 1967 [5], and then in English in 1974 [6].

In his later life, Kawasaki established the Japan Kawasaki Disease Research Center in 1990, and later a nonprofit organization, the Japan Disease Research Center.

Isolation of human angiotensin by Kikuo Arakawa

Angiotensin is the most powerful blood pressure-elevating substance. This peptide hormone is an oligopeptide circulating in the blood. It causes blood vessels to constrict, resulting in elevation of blood pressure, and also causes release of aldosterone from the adrenal cortex. Angiotensin is transformed from the precursor molecule angiotensinogen. It is a crucial molecule in the renin-angiotensin system, which is a major target for drugs that lower blood pressure.

In the late 1930s, angiotensin was isolated in the United States as "Angiotensin," and in Argentina as "Hypertensin," from animal sources. The amino acid composition of angiotensin was first analyzed in animal specimens. Kikuo Arakawa of Kyushu University isolated human angiotensin and determined the amino acid composition of human angiotensin I in 1967 [7]. Subsequently, it was characterized and synthesized by the Cleveland Clinic and Ciba Laboratories in Basel, Switzerland, in 1968.

Following his work on angiotensin, Arakawa was promoted to Professor and Chair of Internal Medicine at Fukuoka University. He presided over the International Society of Hypertension in 1994.

Research on statins by Akira Endo

Statins are a class of drugs prescribed for lowering cholesterol levels by inhibiting the enzyme HMG-CoA reductase. Increase in serum cholesterol concentration accelerates atherosclerosis and coronary stenosis, which then provokes ischemic diseases. Statins are therefore used in the prevention of ischemic vascular diseases. Many clinical trials have shown that statins are effective in preventing and treating cardiovascular diseases. They are also used extensively in people without cerebrovascular diseases but with high cholesterol and other risk factors, such as diabetes and high blood pressure. In 1973, Akira Endo developed the first statin, ML-236B.

Endo, born on a farm in 1933, had an interest in fungi. He earned his PhD in biochemistry from Tohoku University in 1966. He worked at the chemical company Sankyo Co., spending 2 years at the Albert Einstein College of Medicine as a research associate working on cholesterol. He hypothesized that fungi used chemicals to prevent the growth of parasitic organisms by inhibiting cholesterol synthesis. Cholesterol is essential for the synthesis of ergosterol, a fungal cell membrane component. Surveying more than 6,000 compounds from *Penicillium citrinum*, Endo discovered mevastatin (ML-236B), the first member of the statin class of drugs [8]. This study led to the development of other statins. Many statins have since been discovered, and this category of drugs remains a bestseller in the world pharmaceutical market.

Endo was an associate professor, and later a full professor, at the Tokyo University of Agriculture and Technology between 1979 and 1997.

Identification of endothelin by Masashi Yanagisawa

Endothelin (ET-1) is a 21-amino-acid vasoconstrictor peptide that is produced by the vascular endothelium from

a 39-amino-acid precursor, big ET-1, by the actions of an endothelin-converting enzyme found on the endothelial cell membrane. In 1980, Robert F. Furchgott discovered that the process of acetylcholine-mediated vasodilation requires the presence of intact endothelial cells through the release of a dilator factor called EDRF (endothelium-derived relaxing factor). In 1982, De Mey and Vanhoutte reported the release of vasoconstricting factors from endothelial cells. Inspired by these researchers, Tomoh Masaki attempted to identify these substances. Masashi Yanagisawa, a member of Masaki's laboratory, identified a vasoconstricting factor and the sequences of the gene [9]. They named the molecule endothelin for its endothelial cell origin. ET-1 formation and release are stimulated by several substances, such as angiotensin II, antidiuretic hormone (ADH), thrombin, and cytokines. The production is also stimulated by shearing forces acting on the vascular endothelium.

Shortly after the cloning of endothelins (ETs), which include ET-1, ET-2, and ET-3, their cellular targets were identified. Two endothelin receptors (ETA and ETB) mediate ET actions in mammals. Based on biochemical studies regarding endothelins, an inhibitor against endothelin receptors, known as "bosentan," was developed. This medicine is now clinically available for the treatment of pulmonary hypertension. Recently, Yanagisawa has been working on orexin, a neuropeptide, at the University of Texas.

As an anesthesiologist working on medical investigations, I am proud of these frontrunners, who accelerated progress in medical science and whose endeavors have helped countless people worldwide. However, these pioneers were not aiming for heroism. Day after day, they tirelessly and diligently undertook routine experiments that to some of us might seem boring and laborious. Their success stories truly remind us that "There is no royal road to learning."

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