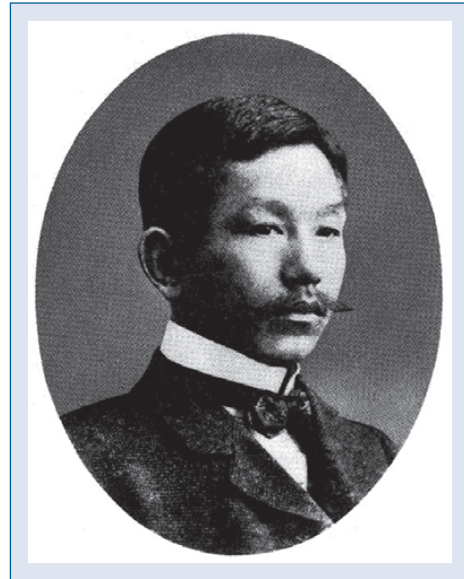


## Sunao Tawara: Discoverer of the atrioventricular conduction system of the heart

At the dawn of the 20<sup>th</sup> century, when the electrocardiograph (ECG) had just been invented by Willem Einthoven and his colleagues, the mechanism by which four cardiac chambers contract synchronously as a cohesive unit remained unknown. Two theories predominated: the myogenic theory and the neurogenic theory [1–4]. The discovery by Sunao Tawara of the atrioventricular (AV) conduction system, reported in a monograph in German in 1906, not only solved the problem of the mechanism for a synchronous contraction of four cardiac chambers, but also gave Einthoven and other electrocardiographers a powerful theoretical basis for interpreting the electrocardiogram. Tawara's discovery of the AV conduction system aided the rapid popularization of the electrocardiograph [3, 5–7]. Tawara was truly ingenious in two particular ways: firstly, in his ability to precisely predict the physiological role of a signal conducting pathway played by the elaborate tree-like structure between the atria and ventricles, which was defined by him as 'stimulus conduction system'; and secondly in assuming that, after a slow conduction through the AV node, signals from the atria could be delivered at a high conduction velocity via right and left bundles nearly simultaneously to the various sites of the ventricles to achieve effective pumping action [3–6]. All of the predictions he made for the functionality of many components of the AV conduction system were subsequently validated by modern cardiac electrophysiological and electron microscopic techniques [3, 4]. His extraordinary and pioneering work on the AV conduction system laid the foundation for modern cardiology and still serves as an invaluable reference and research tool for basic and clinical research (Fig. 1) [3, 4].

Sunao Tawara (1873–1952) was born in the Oita Prefecture of Japan's southernmost island, Kyushu, on July 5, 1873, the eldest son of Sadao and Sai Nakashima. A bright young man, at the age of 15 he was adopted by his physician uncle (the husband of his mother's sister), and took his surname of Tawara. He attended the First College of Tokyo University, and graduated from the Tokyo University School of Medicine at the age of 28 in 1901. For one year after graduating, he studied first dermatology and



**Figure 1.** Sunao Tawara, MD, at the age of about 30.

then internal medicine at Tokyo University Hospital. Thereafter, he practiced dermatology at his father's clinic in Oita Prefecture for a year. However, his intense interest in advancing his medical skill and knowledge finally persuaded his father to financially support him to study in Germany, then one of the most advanced nations for basic medical science.

Shortly after Japan opened its doors to the west in 1868, she made a decision to introduce a western system of law, military, science and medicine. She chose to adopt the German-type system rather than the British style. So, at the School of Medicine at Tokyo University, the nation's foremost university, Tawara learned from German professors and was enormously impressed by the advances in German medicine. It was common in those days that aspiring young Japanese physicians chose Germany to further their medical studies.

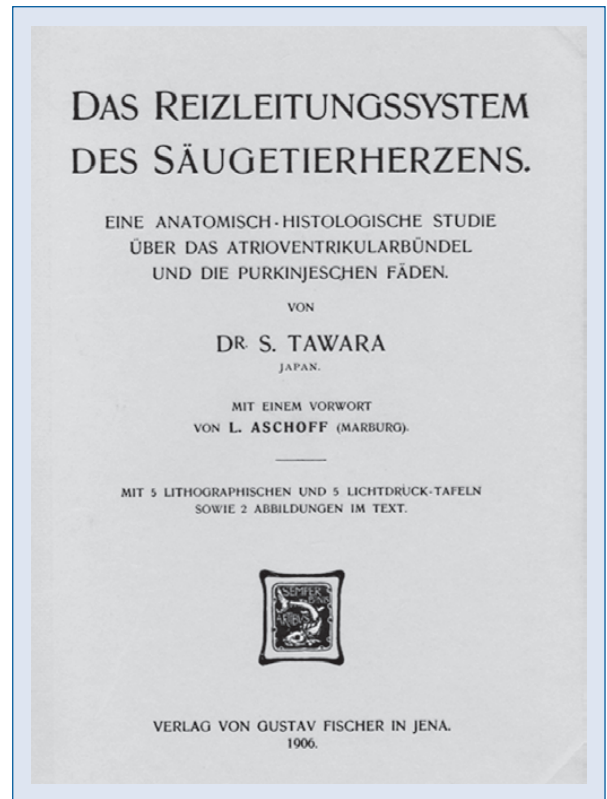
During his short stay in Berlin in 1903, when he was deciding whether to study clinical medicine or pursue basic medical research, he met his medical school senior Keisaku Kokubo, who had just completed a doctoral study with Professor Ludwig

Aschoff in Göttingen. When Tawara learned from Kokubo that Aschoff was a great scholar in pathology and had been appointed Professor at the Institute of Pathological Anatomy in Marburg, Tawara immediately applied to conduct basic cardiac researches at the laboratory of Professor Aschoff, who accepted Tawara as his research fellow. The first assigned research project of Tawara was to carefully examine microscopically 120 hearts, obtained at autopsy, for any evidence of interstitial myocarditis playing a role in cardiac failure. Tawara saw no such evidence as a cause of cardiac failure, but instead he discovered perivascular inflammatory nodules in the hearts of the patients who had died from rheumatic fever. An article about these nodules, which are considered pathognomonic of rheumatic myocarditis, was published in a monograph by Aschoff and Tawara, and since then this nodule has been known as the Aschoff nodule [8].

Because they saw no evidence of interstitial myocarditis causing cardiac failure, Aschoff suggested that Tawara continue his research by examining if the muscle bands discovered in 1893 by His were related in any way to cardiac failure. His, who had discovered this muscle bundle, assumed it directly united the atria to the base of the ventricular septum. Although His thought this bundle conducted the impulses from the atrium directly to the base of the ventricle, he was uncertain as to its function [3, 4, 9]. Tawara intended to trace proximally and distally from the His bundle in various mammalian and human hearts, but the description by His was not sufficient for him to easily locate the His bundle. In addition, distally from the His bundle, when he was able to locate it, there were groups of mysterious large-caliber cells. He encountered great difficulty in proceeding with his new research.

But one day he realized that the Purkinje fibers discovered in 1839 might be connected with the His bundle, and that these two independently discovered fibers might be for the purpose of impulse conduction, and that the mysterious cells he had observed in his research might have been Purkinje fibers [3, 4, 10]. The function of these large gray gelatinous fibers found in the subendocardium of the sheep heart, however, remained uncertain, although there were as many as 30 published theories for the function of these unusually shaped cells [3, 4, 10].

Initially, Tawara found it difficult to locate the Purkinje fibers in the hearts of most mammals, including humans. Therefore, he decided to study the sheep hearts, which had been used by Purkinje in discovering these large gelatinous cells [11]. After he became sufficiently familiar with the morpholo-

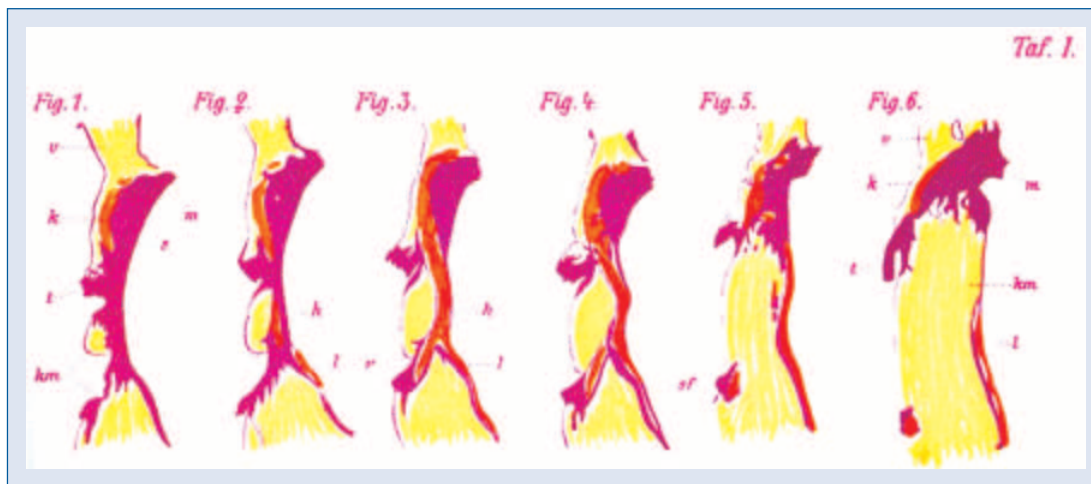


**Figure 2.** Cover page of Tawara's monograph on the stimulus conduction system published in German in 1906.

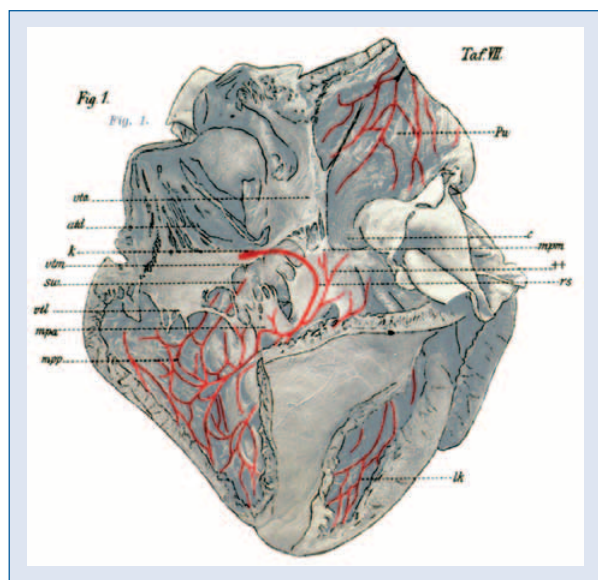
gy of the Purkinje fibers located in the subendocardial layers of sheep hearts, he shifted his attention to the hearts of other mammals, including humans, in which he was now able to identify the Purkinje fibers (Figs. 2–5).

From then on, he was able to trace proximally from the Purkinje fibers to the right and left bundles, which, he found, were connected to the His bundle [5]. Thereafter, he found that the His bundle was connected proximally to a compact meshwork of fibers (which he called a 'knoten', node, in his book). This is the atrioventricular node. Moreover, he was able to show interdigitating connections between the Purkinje fibers and ventricular muscles, as well as between the node and atrial muscles (Figs. 6–8). In this laborious process, he succeeded in identifying a complete discreet pathway, starting from the atrial muscles and ending at the ventricular muscles, which he named in German 'Reizleitungssystem' — stimulus conduction system [5]. This historic work was completed at the relatively young age of 33 [5, 6, 9].

This monumental discovery and insight, made in just three years, is introduced by his statement: "I intend, for the first time in medical history, to

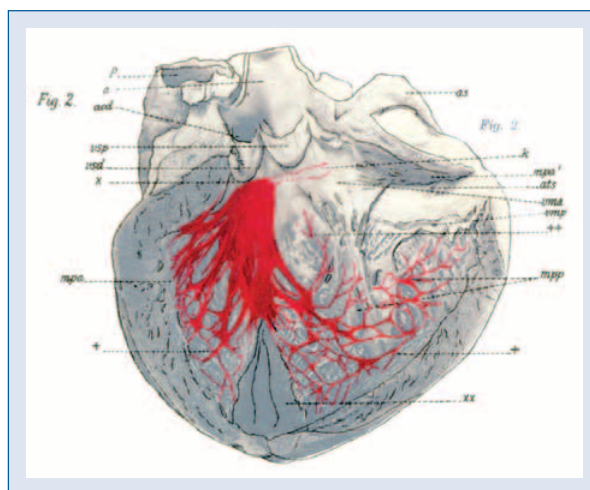


**Figure 3.** Serial cross sections at the base of a human heart revealing the atrioventricular node (k for knoten, node), distally connected to the initial portion of the ventricular bundle (i, the His bundle), then dividing into the right bundle (r) and left bundle (l). Also, anterior mitral leaflet (m), septal leaflet of the tricuspid valve (t), musculature of the atrial septum (v) are shown.



**Figure 4.** Conduction pathway from the atrioventricular node (k), to the His bundle, the right bundle (rs), and then to the right ventricular muscles in a human heart.

propose an integral and consistent explanation concerning the atrioventricular bundle and the Purkinje fibers.” [3–6]. The atrioventricular node, discovered by Tawara, and the bundle distal to the AV node, discovered by His and with its function defined by Tawara, have been called different things in different countries, the former the atrioventricular node (AV node), Tawara’s node, Aschoff-Tawara node, or

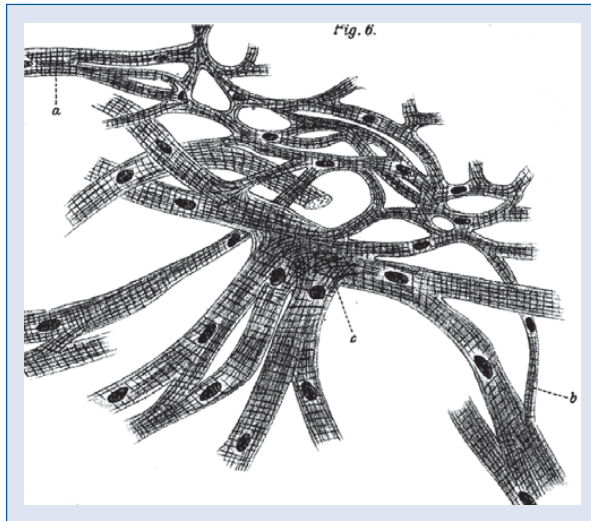


**Figure 5.** Left bundle fanning widely in the left ventricular subendocardial layer of the interventricular septum of a human heart; k — atrioventricular node; vsd — right coronary leaflet of the aortic valve; vsp — noncoronary leaflet of the aortic valve; mpa — anterior papillary muscle; mpp — posterior papillary muscle; vma — anterior leaflet of the mitral valve; vmp — posterior leaflet of the mitral valve; + — dividing site of the connecting bundle (the His bundle); ++ — terminal ramifications of the connecting bundle.

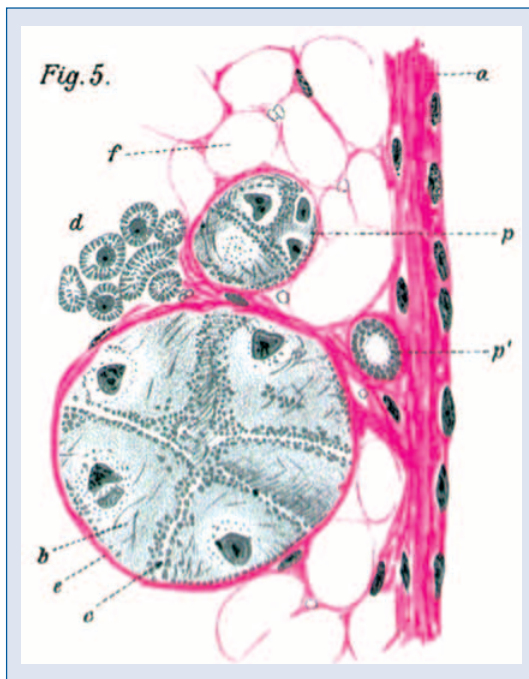
Tawara-Aschoff node, and the latter as the bundle of His, or the bundle of His-Tawara.

Enthused by the publication in 1906 showing the discovery of the atrioventricular conduction system, Keith and Flack in the UK launched a sys-

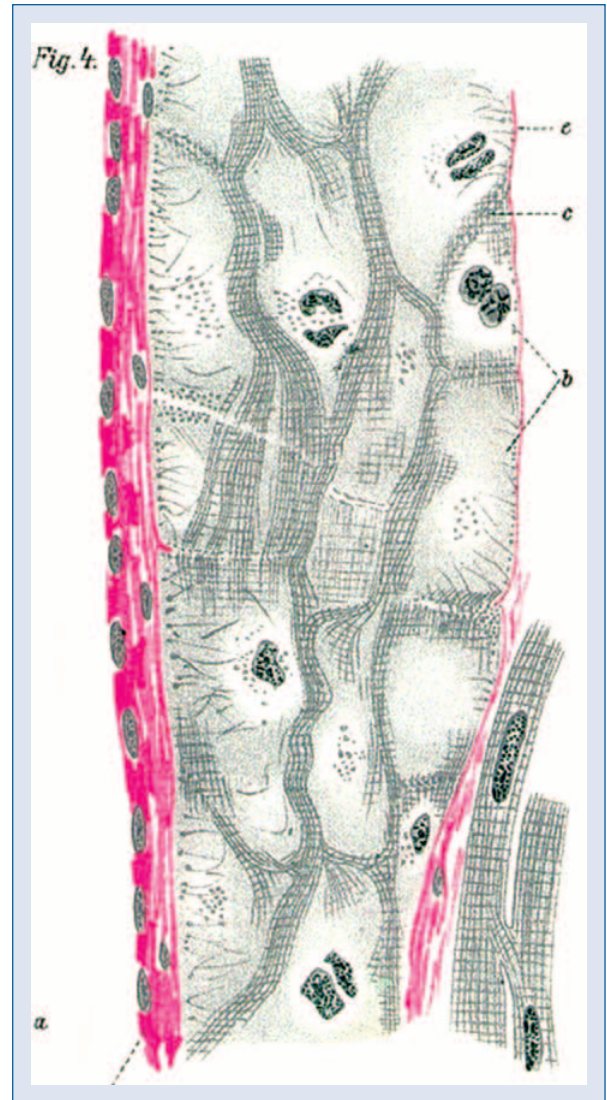




**Figure 6.** Interweaving connections between the atrioventricular nodal cells (slender fibers located at the top right section) and atrial muscles (larger diameter fibers marked as a and c). Thin fibers also connect the two fiber groups (b). At the point marked by c, dense connections exist.



**Figure 7.** Cross-section of the cords of Purkinje fibers of the sheep heart. Connective tissues are drawn in red. In this drawing, the endocardium runs vertically along its right margin, and three Purkinje fiber cords are depicted, each encased completely in connective tissue sheaths; b, p, p' — Purkinje fiber cords containing different numbers of fibers; a — endocardium; c — cell borders; d — cross-sections of the ordinary ventricular muscle fibers (note they are much smaller than the Purkinje fibers); f — subendocardial fatty tissue.



**Figure 8.** Longitudinal section of the terminal Purkinje fibers (b) connect with ventricular fibers (thinner slender fibers running vertically along the right lower section). Other notations: a — endocardium (the red long band running vertically at the left margin); c — cell border; e — connective tissue sheath of a Purkinje fiber.

tematic search to locate a pacemaker area of the heart. They were successful in locating a node at the anterior junction of the superior vena cava and the right atrium, and published their results in 1907 [12, 13]. With this discovery of the sino-atrial node, the atrioventricular conduction system was completely defined, extending from the sino-atrial node to the ventricular muscles.

What then was the significance in medical history of Tawara's discovery of the AV conduction system? It is summarized below based upon opinions expressed in recent publications and this author's personal view.

1. Identifying the myogenic theory to be correct, by clearly demonstrating an integral tree-like structure between the atrial and ventricular muscles, i.e. the stimulus conduction system, in mammalian hearts including the human heart.
2. Unequivocal demonstration that the fibers of the conduction system, especially the Purkinje fibers, are thoroughly encased in connective tissue sheath, thus insulating the conduction fibers from the surrounding working atrial or ventricular fibers (Figs. 6–8).
3. Providing Einthoven and others with the theoretical basis for the interpretation of the ECG waveforms, which promoted the rapid spread of electrocardiography.
4. Providing an anatomico-physiological foundation for the electrocardiographer and cardiac electrophysiologists in understanding the mechanisms of various cardiac arrhythmias and tachycardia.
5. Describing the precise location of all the components of the AV conduction system and the histology of each conduction fiber, thus facilitating the identification of these conduction system structures by subsequent researchers.
6. Identifying the His bundle, Purkinje fibers, and false tendons (free running Purkinje strands within the ventricular cavity) as components of the AV conduction system.
7. Precise description and drawings of the histology of each component of the AV conduction system.
8. Accurate prediction of the conduction velocities of each component of the AV conduction system. Prior to Tawara's publication, conduction via the bundle of His was assumed to be very slow, responsible for a time lag between the onset of atrial contraction and that of ventricular contraction. In those days, the His bundle was considered to connect directly to the base of the interventricular septum. Instead, Tawara suggested a slow conduction taking place in the AV node, and very fast conduction via the His bundle and right and left bundles.
9. Accurate prediction of the very fast conduction velocity of the fibers of the right and left bundle, in order to have most parts of the ventricles simultaneously activated. Furthermore, Tawara's prediction that this near simultaneous activation of most parts of the ventricles is required for efficient cardiac pumping action appears almost to predict the era of cardiac resynchronization therapy.
10. Proving wrong the previous assumption that the His bundle was inserted into the base of the ventricle, meaning that the impulse exiting from the distal end of the His bundle was activating the basal ventricle first and the apical portion at the end. Instead, the terminal Purkinje fibers of both bundles were shown to be connected to the ventricular muscles, with the initiation of ventricular activation there.
11. All of his anatomical and physiological assumptions were later proved correct.

Indeed, the co-discoverer of the sino-atrial node, Sir Arthur Keith, wrote in his autobiography: "With the discovery of the conduction system of Tawara, heart research entered a new epoch." [4, 12, 13]. The discovery of the conduction system by Sunao Tawara has been described as "monumental" by Silverman, Grove, and Upshaw, and he has been called a "father of modern cardiology" by Suma [3, 4].

Soon after his return to Japan in 1906, he was appointed Associate Professor of Pathology at Fukuoka Medical School, newly established in 1903 as a branch of Kyoto National University. Incorporating Fukuoka Medical School at its core, Kyushu National University was established in 1908, where Tawara was immediately promoted to Professor of Pathology, a position he held until 1933. He was appointed Dean of Kyushu University School of Medicine for two years and was twice president of the Japan Society of Pathology. In 1914 he received the Imperial Prize of the Japan Academy for his brilliant work on the conduction system of the heart and given a special medal by the Emperor [4, 10]. He has been considered the main person responsible for making Kyushu University School of Medicine one of the most productive institutions for medical research in Japan.

However, Tawara was raised to study and work hard, but to speak only when necessary. It is well known that he seldom spoke about his own achievements in public or indeed at home. Only in response to persistent requests by colleagues and students would he reminisce and talk about his work and the time when he discovered the conduction system at the laboratory of Ludwig Aschoff in Germany. Tawara died in 1952.

To bring Tawara's work published in German in 1906 to a wider audience, it was translated in 2000 into English by K. Suma and M. Shimada [6].

This author regards Tawara's discovery of the AV conduction system in advancing cardiology, particularly cardiac electrophysiology and electrocardiography, as of an importance equal to that of the

discovery of the circulation of the blood by William Harvey and to the experimental and theoretical studies by A.L. Hodgkin and A.F. Huxley on the initiation and spread of excitation in nerves, which was later successfully reproduced in cardiac and other excitable cells [14–20].

Some of the descendants of Sunao Tawara are themselves physicians and his birthplace in Oita Prefecture, Kyushu has been meticulously preserved. It is my hope that Sunao Tawara posthumously receives the award of Nobel Prize in Medicine, which he abundantly deserved during his life.

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*Toshio Akiyama, MD, Professor Emeritus  
of Medicine (Cardiology)*

*University of Rochester Medical Center, Rochester,  
New York 14624, USA  
14531 Quail Rock Court, Reno, Nevada 89511, USA  
tel: 775 853 1558, fax: 775 853 1728  
e-mail: takiyama1558@charter.net*

