Tigerstedt and the Discovery of Renin

An Historical Note

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RENIN was discovered at the Karolinska Institute in 1898 by Robert Tigerstedt, a noted physiologist, and Per Bergman, his 24-year-old student. This discovery, a result of model scientific method in action, lay dormant for 40 years before its importance was first appreciated. Once appreciated, the awareness of a renal pressor substance led to thousands of major researches and far-reaching findings that immeasurably advanced medical science, especially in the approach to patients with hypertension. Thus, the discovery of renin ranks as a landmark in the history of medicine, and it is remarkable that the story of this discovery has not been presented heretofore.

Robert Adolph Armand Tigerstedt (fig. 1) was born February 28, 1853 in Helsinki, Finland where his father, Karl, was a history professor. Robert's basic education at the University of Helsinki was in the physical and natural sciences, particularly in chemistry because of the influence of his teacher, the famed C. J. Arrhenius. At the University of Helsinki, Tigerstedt studied medicine from 1876-1880, not with the intention of becoming a practitioner, but because of his interest in research in natural science. During this period he maintained an active interest in the basic sciences, particularly physiology. Gustav Retzius was his trusted adviser in medical school, and he later influenced Robert to move to Stockholm. While a medical student, Robert married his cousin Ljuba Martinau, a Ukrainian, and their first child, Maria (1879-1976), was born before his graduation. After completing his medical education, Tigerstedt had hoped to remain in Helsinki in an academic appointment. However, his doctoral dissertation ("On the Mechanical Stimulation of the Nervous System") displeased Hallsten, the professor of physiology at the university there, and Tigerstedt was forced to look elsewhere for employment. By chance, a position had opened at the new physiology department in Stockholm. His friend Retzius intervened in his behalf with the Swedish physiologist, Christian Loven, first chairman of the physiology department at the Karolinska Institute (and best known for his discovery of the taste buds); in 1881, Tigerstedt was named demonstrator in experimental physiology at the Karolinska. There he remained for the next 20 years, first as assistant to Loven, then after 1886, when Loven retired, as professor. During this time, Tigerstedt first began to wonder about a renal pressor substance.

The 20 years Tigerstedt spent at the Karolinska from 1880 to 1900 were extremely productive, and he would have been a very famous physiologist even had he not discovered renin. First, he established a well-equipped laboratory, which previously had been lacking in that part of the world. One of his students later described Tigerstedt’s laboratory as follows. "In this laboratory there was the most lively activity. It was remarkable how exciting it was, what a marvelous tempo and vitality characterized the work there. And everywhere the boss himself was present, encouraging, helping, criticizing, and discussing ... as a rule with a cigar in his mouth, often full of fun and mischief."

While at the Karolinska, Tigerstedt wrote his Textbook of Human Physiology which was published in five languages and went through 10 editions over a 26-year period. It was the authoritative work in physiology at the time. His friend Pavlov, the Russian physiologist, wrote the preface, calling it the greatest textbook of physiology ever written. Tigerstedt was editor of four different journals at the same time. He wrote extensively in popular magazines, and one essay, a pamphlet on alcoholism, was so popular that nearly 200,000 copies were issued. He had a profound respect for history (undoubtedly inherited from his father), and he published commemorative works on many famous scientists including Harvey, Vesalius, Lavoisier, Helmholtz, and Ludwig. When Alfred Nobel died in 1896, Tigerstedt was asked to help draw
up the basic principles for the Nobel Foundation at the Karolinska. He was still an active member of the Nobel Committee in 1912 when the Prize in Medicine and Physiology was first awarded to a surgeon, Alexis Carel, for his pioneering work in vascular surgery.

Despite Tigerstedt’s many other achievements, it was his discovery of renin that gained him an enduring spot in medical history. His interest in a renal pressor substance was apparently stimulated by the work of three earlier scientists: Richard Bright (1789-1858) of England, Karl Ludwig (1815-1895) of Germany, and Charles Brown-Séquard (1817-1894) of France.

Bright was the first to link kidney disease with hypertension when he made the observation that patients dying with contracted kidneys often exhibited a hard, full pulse, and cardiac hypertrophy. Well aware of Bright’s work, Tigerstedt states in the introduction to his famous study: “As far as we know, no one has yet investigated to what extent a substance influences the circulatory organs from the kidneys. In view of the intimate connection between some renal and cardiac diseases, it seemed possible to investigate the presence of such a substance.”

Ludwig, the pre-eminent teacher of physiology during the 19th century, first interested Tigerstedt in blood circulation. In 1847, Ludwig added a float to Poiseuille’s mercury manometer and recorded blood pressure on a revolving kymograph, which remained for the next 100 years the classic method of blood pressure recording in the laboratory. To Ludwig’s laboratory in Leipzig, aspiring physiologists from all over the world came for research and study. Tigerstedt is known to have visited Ludwig in Leipzig in 1881 and 1884. Tigerstedt’s laboratory in Stockholm was modeled after that of Ludwig, and when the former retired many years later, his farewell speech was simply entitled, “Ludwig.”

The influence of Bright and Ludwig notwithstanding, it was Brown-Séquard, the father of modern endocrinology, who most directly stimulated Tigerstedt to discover renin. Brown-Séquard was the successor of Claude Bernard at the Sorbonne in Paris. Brown-Séquard was the author of the doctrine that many organs dispense substances into the blood which are not ordinary waste products, but have specific functions. A corollary of this doctrine was that a deficiency of any one of these “chemical messengers” would result in certain disease states.

On June 1, 1889, Brown-Séquard, then a famous man of 72, rose before the Société de Biologie of Paris and announced to the world that he had given himself during the previous 2 weeks subcutaneous injections of a guinea pig testicle extract. The result was complete rejuvenation. In his own words, “I have regained my vigor . . . and all my troubles have completely disappeared.” This announcement and the work which followed went through the medical world like a shot. The lay press sensationalized the results, and by the end of that same year, more than 12,000 physicians were busily administering the testicular extract to their patients.

In the wake of his original experiments, Brown-Séquard investigated the effects of other organ extracts, one of which was a renal extract he gave to nephrectomized animals. The result seemed to be a temporary improvement in their condition. He concluded; “Uremia (and jaundice), like tetany after removal of the thyroid, depend in part on the absence in the blood of certain principles, which an injection of renal (or hepatic) fluid could cause to disappear.” Thus was Tigerstedt stimulated in 1896 to begin an investigation of the effect a renal substance might have on the circulation. The result, published in 1898, was a perfectly planned and executed study, “Niere und Kreislauf” (Kidneys and Circulation), simple but elegant, and so far ahead of its time that it took the scientific community 40 years to appreciate it.

The basic hypothesis of Tigerstedt and Bergman was that “... a blood-pressure raising substance is formed in the kidneys and passed into the blood.” To test this hypothesis, the investigators homogenized fresh rabbit kidney in saline, centrifuged this material, and then injected the supernatant fluid into other rab-
bits. Almost always, the kidney extract injections resulted in an increase in blood pressure in the recipient rabbits (Fig. 2). The extraction process was identical to the one Brown-Séquard used to obtain his testicular extract. The method of monitoring blood pressure, although not stated, was almost certainly the kymographic method Tigerstedt learned from Ludwig. The investigators demonstrated that the same pressor substance was present in renal venous, but not arterial blood. They also demonstrated that the active principle in the extract was none of the known substances present in urine. Instead, it seemed to be a "substance sui generis," i.e., something unique. Thus, the hypothesis was supported by the data. Furthermore, Tigerstedt and Bergman state, "We wish to call this substance for the sake of brevity by the name renin." The investigators may be fairly credited with both discovering and naming renin.

Tigerstedt and Bergman made a number of important and correct observations about the nature of renin. First, they noted it to be an extremely potent pressor agent, even in very small quantities. Just a fraction of a milliliter of the extract would raise a rabbit's blood pressure by 25% to 50%. The investigators found renin to be water soluble, non-dialyzable, and heat labile, all of which suggested that renin is a protein. Renin could be extracted from renal cortex and renal venous blood, but not from renal medulla or renal arterial blood. With repeated injections, there was a decreasing effect on blood pressure (tachyphylaxis). With regard to mechanism of action, Tigerstedt and Bergman observed that section of various nerve centers (bulbar, medullary, spinal cord and cardiac) had no effect on the pressor action of renin; nor was heart rate affected by renin. Therefore, the pressor action appeared to be mediated by an effect on vascular smooth muscle, though not necessarily a direct effect.

All of the foregoing observations are compatible with modern knowledge of renin, i.e., that renin is a proteolytic enzyme of approximately 40,000 molecular weight, synthesized by the juxtaglomerular cells of the renal cortex, the sole action of which is to cleave a leucine-leucine bond on renin substrate and liberate angiotensin. The direct pressor substance in the system, angiotensin, was discovered during the late 1930's concurrently by Irvine Page and his associates in the United States and by Eduardo Braun-Menenez and his colleagues in South America. Subsequently, angiotensin was isolated, characterized structurally and synthesized. Renin, however, has not yet been isolated in pure form and its structure is yet to be determined.

In drawing conclusions from their data, Tigerstedt and Bergman were quite cautious: "... with these observations, we do not formulate a new hypothesis about the interconnection between renal diseases and cardiac hypertrophy. ... We only wish to draw attention to the possible importance of a blood pressure-raising substance formed in the kidneys."
authors did suggest that: "under certain circumstances, this substance (renin) could be formed in larger quantities than usual. . . . In that case there would be exerted a stronger and more lasting action than under normal circumstances upon the vascular musculature, and in this manner the resistance in the vessels could be constantly raised above the normal level. Hypertrophy of the heart would be a result of this." No subsequent statement describes the mechanism of vasoconstrictor hypertension any better than the above.

Although there were subsequent investigations on renin and experimental hypertension, widespread interest in renin did not occur until after Harry Goldblatt opened the door to renovascular hypertension in the 1930's. In Goldblatt's monumental work, he showed that experimental hypertension could be produced by renal artery constriction, and he speculated that in this condition: "there may be an accumulation or new formation of some substance . . . which may effect a pressor action like that of a hormone." Interest in renin was then re-awakened with a start. In 1938, three separate groups published confirmation of Goldblatt's work. However, on December 2, 1923, in his native city of Helsinki, Tigerstedt quietly had died in his sleep at the age of 70. Thus, never in his lifetime did he enjoy compensation or accolade for his momentous discovery.

Further interest in renin paralleled the appreciation of human renovascular hypertension, which was unknown before Goldblatt. The urologist, Hugh Young, in his 1940 autobiography, states, "... the first demonstration and cure of the condition produced by Goldblatt was in a case at the Brady Institute four years ago. His (the patient's) blood pressure had rapidly increased to 200. . . ." An adrenal tumor was suspected, but during exploration of the retroperitoneum, a renal infarction was discovered. The kidney was removed. "The operation was followed by an amazing result. The blood pressure that had been so high promptly fell to less than normal. In a few days, the eyesight began to improve. Now, two years later, he has practically normal eyesight, and has been completely relieved of the hypertension. The terrific headaches disappeared very soon after the operation, and they have not recurred.

In this case the conditions found in the kidney were practically identical with those produced by Goldblatt with clips upon a renal artery. For the first time it was shown that by removal of one kidney that was found to be the subject of arterial disease, hypertension that had baffled medical science for generations could be cured."

There followed four decades of intense research in renin and hypertension, the results of which have been summarized by Oparil and Haber. The recent development of specific blocking agents have led to the conclusion that in most cases of human renovascular hypertension, and certain cases of essential hypertension, overactivity of the renin-angiotensin system is a major pathophysiologic factor.

Two years after publication of "Niere und Kreislauf," Tigerstedt, then age 48, left the Karolinska Institute and returned to Finland. Hallsten, his old adversary at the University of Helsinki, had finally stepped down, and Tigerstedt was given the chair in physiology. Tigerstedt's return was something of a major national event because Finland was then struggling for independence from Russia, and the outlook at that time was not good. Thus, when one of the most respected scientists of the day gave up a secure position abroad and returned to his homeland with all its uncertainties, a great boost was given to Finnish nationalism. Finland eventually did win independence in 1918, the same year that Tigerstedt voluntarily retired at age 65. What he regarded as his magnum opus, a 1500 page text, The Physiology of Circulation, was completed five years later, shortly before his death. Robert's son, Carl (1882-1930), succeeded him as professor of physiology; however, Carl died in a sailing accident at the age of 49. Carl's son, Lars (1911), a recently-retired general practitioner, lives today in Anaset, Sweden, and he serves as the family historian. Greta Tigerstedt (1891), Robert's third child, lives in Helsinki. Per Bergman, the medical student who co-authored "Niere und Kreislauf," spent the remainder of his life as a general practitioner in Malmo, Sweden, and died in 1957.

According to one medical historian, Tigerstedt's discovery of renin would have warranted a Nobel Prize, had the importance of the discovery been recognized at the time. But it was not; even Tigerstedt himself failed to see the importance of his own work. The timing was simply not right for it, and he never performed follow-up studies. Thus, when Tigerstedt died in 1923, his obituaries published the next year in many leading European journals, made no mention of renin. The importance of renin was to await the works of Volhard, Goldblatt, Pickering, Page, Braun-Menendez, Peart, Laragh, Davis, and many others who came years later. However, the start of this chain was clearly Tigerstedt, who was first to ask and answer the question, "Is there something made in the kidney which can influence the circulation?"

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