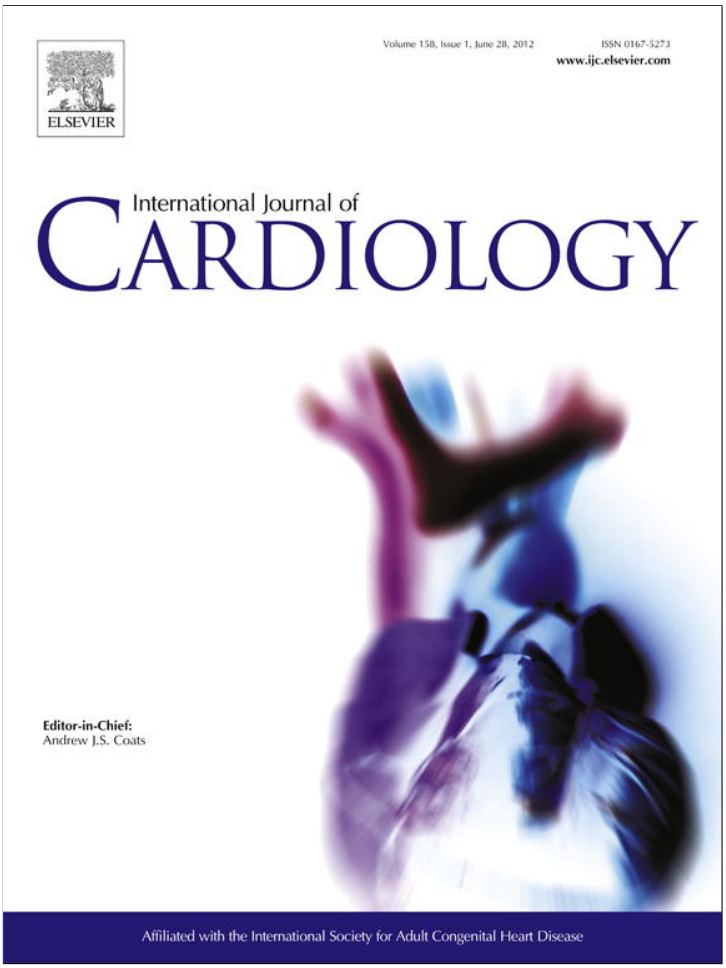

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Editorial

Robert Tigerstedt and the discovery of renin — A revisit

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'Renin', the proteolytic polypeptide was discovered by Robert Adolph Armand Tigerstedt and Per Gustav Bergman in 1898. The discovery of renin was the first step in the understanding of long term regulation of blood pressure. However, the prime importance of renin was brought into limelight almost 35 years after its initial discovery. The experiments conducted by Tigerstedt and Bergman were very elegant and difficult to duplicate. They were followed by the experiments of many eminent scientists like Franz Volhard, John Loesch and Harry Goldblatt producing renal ischemia which later paved the way for tremendous work on renin and the concept of renin–angiotensin–aldosterone hypothesis. Here we present a brief memoriam of Robert Tigerstedt and the events leading to the discovery of 'Renin'.

Robert Adolph Armand Tigerstedt (1853–1923) (Fig. 1) [1,2] was born in Helsingfors, Finland on the 28th of February 1853, to Professor Karl Konstantin Tigerstedt and Evelina Theresia Degerman. Karl Tigerstedt was a well-known historian. Tigerstedt's basic education was at the University of Helsinki. He studied physical and natural sciences, particularly chemistry. We come to know that he was greatly influenced by his teacher CJ Arrhenius. Later, he studied medicine (1876–1880) in order to pursue his passion for research in natural sciences [2]. He married his cousin, Ljubov Ludmilla Martinau during his medical studies. He obtained his doctoral degree, his thesis topic being "study über mechanisch Nervenreizung" (German) [3] (on the mechanical stimulation of the nervous system). Tigerstedt then graduated from Helsinki and got his licentiate in 1880. He aspired to continue as an academician at the Helsinki University. But, on the advice of his trusted mentor Gustav Retzius, Swedish physician and anatomist, he moved to Stockholm in 1881. Retzius intervened on Tigerstedt's behalf with Swedish physiologist, Christian Loven, known for the discovery of taste buds, first Chairman of Department of Physiology at the Karolinska Medical Surgical Institute, Stockholm, who offered him a position of demonstrator (Privat-dozent/Lecturer) [4] in Experimental Physiology [1].

During his stay in Stockholm, Robert conducted frog muscle nerve experiments. He determined the latent period of the gastrocnemius muscle nerve preparation. This improved his expertise in experimental physiology and was instrumental in his appointment to the Chair of Physiology at Karolinska. Robert remained there for the next 20 years, first as an assistant to Loven, and then became professor in 1886 following the retirement of Christian Loven. It was here that Robert discovered *Renin* [5].

We come to know that Robert Tigerstedt's interest in a renal pressor substance was apparently influenced by the work of three scientists, Carl Ludwig (1815–1895) of Germany, Richard Bright (1789–1858) of England, and Charles Edouard Brown Sequard (1817–1894) of France [2].

Richard Bright first demonstrated a link between hypertension and kidney disease two centuries ago. He wrote "the obvious structural changes in the heart [in patients with shrunken kidneys] have consisted chiefly of hypertrophy with or without valve disease; and, what is most striking, out of 52 cases of hypertrophy, no valvular disease whatsoever could be detected in 34" [6]. He observed that patients dying with contracted kidneys often exhibited hard, full pulse and cardiac hypertrophy. Well aware of Richard Bright's work, Tigerstedt mentions in the introduction to his paper [7] "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 disease, it seems possible to investigate the presence of such a substance" [2].

Carl Ludwig, was one of the most famous cardiovascular physiologists of the19th century. Carl Ludwig was the one who first introduced Robert to cardiovascular research [4]. Ludwig invented a permanent method of recording blood pressure on a revolving kymograph by adding a float to Poiseulle's mercury manometer in 1847 which is still in use in some laboratories. Aspiring physiologists from all over the world visited Ludwig at his laboratory in Leipzig. When Tigerstedt built his new laboratory at Karolinska, he modeled it on the lines of Ludwig's physiology lab [2,5]. At the new laboratory, the focus was on blood pressure stability despite variation in the quantity of liquid in the vascular system, heart function at varying resistance in the arteries, mammalian cardiac nutrition, blood distribution in the body, stroke volume, renal blood flow and the effect of kidney extracts of the blood vessels musculature [3]. He also studied the pulmonary circulation, pulse and vagal effects on the heart [1].

Charles Edouard Brown Sequard is directly credited with the impetus leading to the discovery of renin by Tigerstedt. Sequard in late

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Fig. 1. Robert Adolph Armand Tigerstedt (1853–1923), in his laboratory at the University of Helsinki, circa 1910.

1850s injected extracts from different donor animal organs into other animals and human beings (including himself) and tested their effects. Along with d'Arsonnval, he used kidney extracts in nephrectomized animals and noted how it could improve the animal's condition [8]. Logically it was assumed that a deficiency of these substances resulted in disease states [9]. Brown Sequard announced "I have regained my vigor…and all my troubles have completely disappeared" after injecting himself with guinea pig testicular extracts (Elixir of Life) [10]. This in turn started many experiments by scientists who injected various extracts. In the opening of his paper [7], Tigerstedt describes "The ingenious thought of Brown Sequard" as his inspiration to the study which led to the discovery of *Renin* [2]. Oliver and Schafer then demonstrated that suprarenal gland extracts caused powerful vasoconstriction in animals in 1895 [11].

Other experiments which might have influenced Tigerstedt were done by Grawitz, Israel and Lewinski who occluded the renal arteries of rabbits and dogs respectively and found evidence of "compensatory" cardiac hypertrophy. Lewinski thought that unknown humoral substances, normally excreted by the kidneys, might affect the heart and cause vasoconstriction of small vessels [12]. These were the experiments, which inspired Tigerstedt to begin his experimentation on kidney from where he suspected a chemical to be released which affected the blood pressure.

Robert Tigerstedt was appointed as President of International Congress of Medicine held at Moscow, Russia in 1897. He started his experiments with the assistance of a medical student Per Gustav Bergman on 8th November, 1896. It has even been suggested that the research was carried out only for the purpose of presentation at the Congress [13]. The basic hypothesis with which Robert started was "… a blood pressure raising substance is formed in the kidneys and passed into the blood" [7,14].

To test his hypothesis, the investigators injected fresh kidney extracts in various forms. The first technique consisted of injection of supernatant of centrifuged homogenized fresh rabbit kidney in saline into the jugular vein of other rabbits and recording of the blood pressure once every 10 s and noting the readings [2,15]. The other methods followed were by trying different ways of extracting the kidney substance — using boiling water, boiling the cold water extract, 50% alcohol, glycerine, and absolute alcohol. It was found that the best procedure was to pulverize the kidney in absolute alcohol and after filtration and air drying, solubilize the extract in water or saline. The equipment was probably similar to the one used by Oliver and Schfaer in 1895 [11]. They used a kymograph (to record BP) and mercury manometer invented by Carl Ludwig. Catheterization of the artery was most likely by brass tubes, ligated to the vessel and attached by a saline filled rubber tube to the manometer [14]. Tigerstedt and Bergman conducted about 50 experiments from November 1896 to May 1897 [5].

The results of the experiments showed a consistent rise in blood pressure with each injection of the extract. The increase in blood pressure ranged between 18% and 50%. The first experiment showed an increase of 50% in blood pressure within ~80 s from 62–67 mm Hg to 100 mm Hg. The second extract showed an increase of 25% (103 to 127 mm Hg) and the third an increase of 18% (97 mm Hg 113 mm Hg) (Fig. 2) [2,15].

This was followed by slight variation of the same experiment to confirm their results. Despite the variation of baseline values throughout the study, an increase in blood pressure was invariably observed within a minute of injection of the extract [5]. From the above experiments they concluded that a pressor substance was released from the kidney, which was water and alcohol soluble, non dialyzable, heat labile and destroyed at temperature above 56 °C. These features suggested that the chemical was a protein. 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 Tigerstedt and Bergman made a bold proclamation, "we wish to call this substance for the sake of brevity by the name Renin" [2,16].

Following were the observations made regarding the pressor substance by Tigerstedt and Bergman:

1) Even when injected in small quantities [fraction of a milliliter of the extract (7–17 mg)], renin was extremely potent in increasing BP (by 25–50%) [2,16].

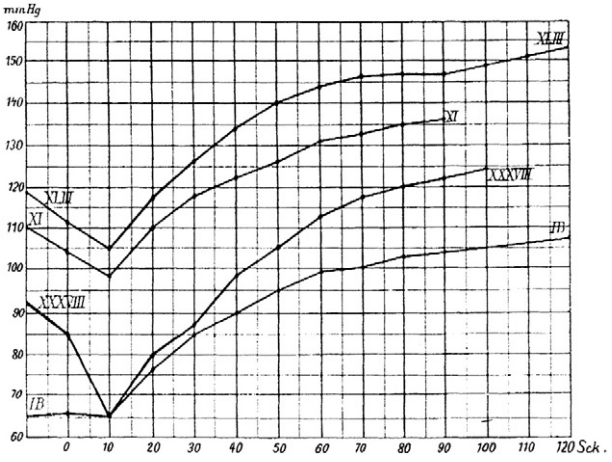


Fig. 2. Tigerstedt and Bergman's experiments demonstrating a pressor effect of crude saline extracts injected into four rabbits. Notice that the blood pressure response was biphasic, with a short-lived decrease and then an increase in blood pressure that was maximal at about 2 min.

2) Renin could be extracted from the renal cortex, but not from the renal medulla [16].
3) Renin was found only in the renal venous blood and not the arterial blood [2].
4) Blood from the renal vessels were effective in raising BP when given to nephrectomized rabbits.
5) There was no increase in heart activity when blood from renal vessels was tested on the heart using Langendorff's technique [16].
6) Tachyphylaxis (decreasing effect of renin on BP) was observed with repeated injections [2].
7) Tigerstedt and Bergman tried to elucidate the mode of action of renin by conducting various experiments. The role of nervous system on pressor action of renin was tested by sectioning various nerve centers (bulbar, medullary, spinal cord and cardiac). It was found that none of these had any effect on the pressor action of renin. The heart rate remained unaffected. So, they postulated the existence of 'peripheral vascular centers' that could possibly mediate the effect of renin on blood pressure. Unfortunately, Tigerstedt and Bergman did not define any further details about these peripheral centers [2,16].
8) Oliver and Schafer (1895) [11] and Szymonowicz (1896) [17] had observed that the suprarenal extracts increased blood pressure by direct contraction of blood vessels. Though there existed the suspicion of the autonomic system being the mediator of renin's action, the exact mode of action of renin was not resolved by Tigerstedt. It was hypothesized that when renin is produced in large quantities and excreted more slowly, it exerted a stronger and long lasting action on the vascular smooth muscles, increasing resistance to blood flow and thus blood pressure, leading to hypertrophy of the heart. The mechanism behind vasoconstriction leading to hypertension was not studied [16].

In a dramatic end to their article [7], the authors have written "… 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." Further studies to learn the mechanism of action of renin were not taken up by the investigators after the battery of experiments done in the span of a year [2].

Tigerstedt presented his findings at the International Congress of Medicine as a long abstract. The work was highly applauded. Tigerstedt and Bergman published all the above findings in 1898 in the Scandinavisches Archiev fur Physiologie, in the article titled "Niere und Kreislauf" (49 pages) meaning 'Kidney and Circulation'. This article is in German language and thus it is seldom read and cited [2,15].

The method used during the experiments was not published in detail in the paper [7]. The lacunae in the study were failure to locate additional sources of renin other than the kidney, to study the effect of renin on other animal species and inability to extract renin in its pure form. Another limitation was that there was lack of statistical analysis then. The data of all the experiments done by Tigerstedt and Bergman were presented in about 51 tables, each containing raw data and about 5 figures (Fig. 3) [16].

However, Tigerstedt's paper holds a unique position in the history of Medicine and Physiology. This paper gives us an insight into the exquisite methodology and the thought processes of the scientists in the 1890s, more than a century ago.

Two years after the publication, Tigerstedt moved to his native, Finland [2]. Bergman left academics to become a physician in Malmo, Sweden. The sad part of the story is that they themselves (Tigerstedt and Bergman) or any other researchers did not do any confirmatory studies. Further the results of the experiments could not be duplicated in other laboratories at that time. This resulted in lack of follow up studies. Thus the extraordinary discovery was almost forgotten for next 30–40 years.

Periods of 10 s	Blood pressure			Number of heart beats per 10 s	Comments
	Maximal	Minimal	Mean		
34	70	64	67	30	
35	70	64	67	30	
36	66	58	62	30	
37	66	56	61	29	Injection of 5 ccm of extract
38	70	62	66	29	
39	70	60	65	30	
40	84	68	76	30	
41	88	82	85	30	
42	94	86	90	32	
43	98	92	95	32	
44	102	96	99	32	
45	102	98	100	33	
46	106	100	103	33	
50	110	106	108	34	

Fig. 3. Experiment 1B, November 8, 1896. A kidney was pulverized with 21 ml of cold water. Injection into jugular vein. Within ~80 s, there is a rise in mean blood pressure from 62–67 mm Hg to 100 mm Hg, i.e., an increase by ~50%. It is obvious that injected volume (5 ml) is not responsible for this rise.

Katzenstein in 1905, Passler and Heinecke in 1906, Bingel, A. and Struass, E. in 1909 and Rauterberg in 1910 [12,18] confirmed the findings of Tigerstedt and Bergman. However, these works were also forgotten soon. Some scientists found different results from that of Tigerstedt. Alwens performed renal compression experiments in 1909 and found elevation in blood pressure. However, he found an increase in blood pressure when he exerted external pressure on other abdominal organs and wrongly concluded that the observed effects were caused by a passive transduction of the applied external pressure to the arterial system. In 1911, Senator induced bilateral partial obstruction of renal arteries of cats but found no increase in systolic blood pressure in these heavily anesthetized cats, and erroneously concluded that diseased kidney with reduced arterial flow could not produce the vasoactive substance described by Tigerstedt and Bergman. Lichtwitz totally rejected the hypothesis that the kidneys release vasoactive substances because he reasoned that the release must be continuous, a task beyond the abilities of diseased kidneys [12].

Ernst Henry Starling, the discoverer of 'Secretin', in his Text Book of Physiology (1933) did not mention anything about renin. In fact, the text book mentioned that the job of the kidney was to excrete urine and had no connection to blood pressure control [19]. In fact 'Renin' can be said to be the first hormone whose activity was discovered. But the word hormone did not even exist in 1898 when Tigerstedt discovered renin.

Thomas S. Kuhn observed that "…science is a series of peaceful interludes punctuated by intellectually violent revolutions…". In 1920s Franz Volhard and his students Hulse, Hessel and Hartwich conducted meticulous experiments and were able to isolate renin in relatively pure form. Hessel suggested that renin was preformed and stored in the kidney and that it was a weaker vasoconstrictor in organ bath. Thus he concluded renin was not causing direct vasoconstriction. Much before Goldblatt, Volhardt, et al., constricted the renal artery of dogs with a band of silver wire, injected blood from renal vein of the ischemic kidney containing renin into normal dogs and observed the development of hypertension [12].

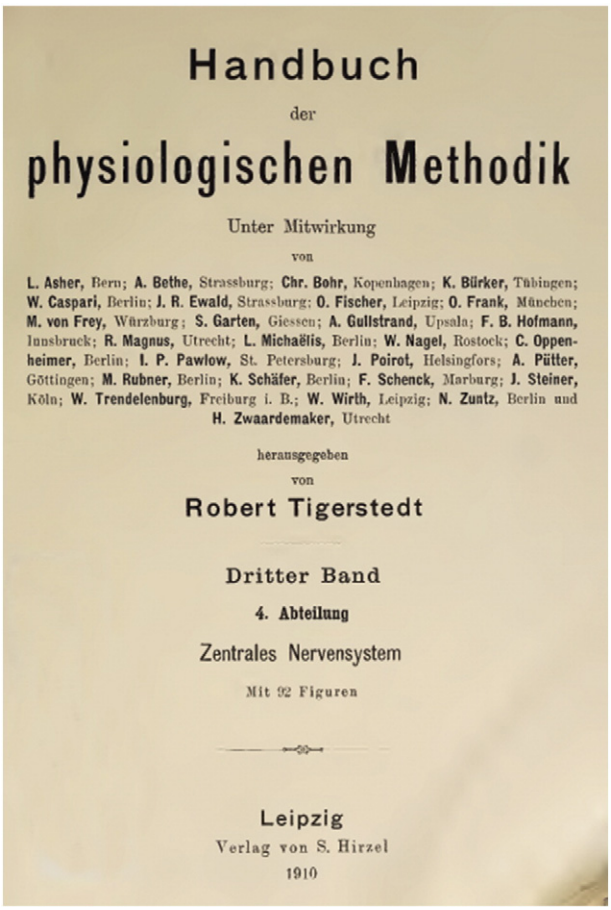
It was finally John Loesch and Harry Goldblatt who published their work on renovascular hypertension in the articles "A contribution to Experimental Nephritis and to Arterial Hypertension" in the German language journal, Zentrablatt fur Innere Medizin (1933) and "The production of persistent elevation of systolic blood pressure by means of renal ischemia" in Journal of Experimental Medicine (1934) respectively, which confirmed the existence of renin and triggered off immense research in the field [20]. The interesting phase of renin angiotensin discovery came in 1939 when 2 different groups (Irvine Page, et al. and Eduardde-Braun Menendez, et al.) studying renin at 2 different places, by conducting different experiments,

elucidated the mechanism of action of renin and gave it 2 different names, Angiotonin [21–23] and Hypertensin [24–26] respectively. Later in 1958 the chief investigators of the 2 groups met and decided on a common nomenclature for the substance with half of letters of their previous names as "Angiotensin" [27]. Elliot and Peart gave the correct sequence of angiotensin [28]. Skeggs et al. described the mechanism involved in the production of Angiotensin II, the chemical causing vasoconstriction and hypertension and Angiotensin Converting enzyme (ACE) involvement in the same [29,30]. Skeggs stated, "As renin is the initial and rate limiting substance in the renin–angiotensin system, it would seem that renin inhibition would most likely succeed in achieving renin–angiotensin system blockade" [31]. Today we are in a stage where hypertensives are treated with ACE inhibitors and recently renin inhibitors (e.g.: Enalkiren, Aliskiren) [32,33].

After his return to Finland, Tigerstedt became the Chair of Physiology at the University of Helsinki and continued research (1895 to 1920) on metabolism, heat production and nutrition [2,4]. He described an illness which could be scurvy. Tigerstedt was energetic, hard working and a scientist dedicated towards research. Tigerstedt's tenure in the University of Karolinska saw the publication of more than one text book of Physiology authored by him. "Lehrbuch der Physiologie des Menschens" a textbook of Human Physiology has been translated in three languages, English, Italian and Russian. His friend Ivan Pavlov, wrote the preface of the book and has mentioned the book to be the greatest Textbook of Physiology ever written. It was one of the authoritative works that dominated Physiology teaching for decades after its publication, appearing in 10 editions (1897 to 1923). The next book was "Handbuch der Physiologischen Methodik" (Fig. 4) [34] which was published between 1910 and 1914 in three volumes. The third book was "Die Physiologie des Kreislaufes" (Fig. 5) [34] ("The physiology of the blood circulation") published in four volumes between 1921 and 1923 while he was at Helsinki [5]. This 1500 page book is a comprehensive compendium of what was known about the central and peripheral circulation then. This book was completed after his retirement from Helsinki, shortly before his demise [2].

When Alfred Nobel died in 1896, Tigerstedt along with Karl Mörner were the Karolinska Institute's delegates in charge of the task of putting Nobel's imprecisely worded will into executable shape. Tigerstedt was involved in the promotion and establishment of the Nobel Prize in Physiology or Medicine. Bertel von Bonsdorff, Professor of Internal Medicine at the University of Helsingfors, in his biography [35] on Tigerstedt has said that, the discovery of renin would have fetched him the Nobel, had he himself known the importance of his discovery. In fact, the Nomination Database for the Nobel Prize in Physiology or Medicine, 1901–1953, shows Robert Tigerstedt as one of the Nominees in 1919 [36]. Tigerstedt's work in "Die Physiologie des Kreislaufes" fetched him another Nobel nomination in 1923 [37].

Tigerstedt's return to Finland was at the right time, when Finland was struggling for its independence from Russia. He was active in improving nutrition and the quality of food for working people. He promoted international co-operation among scientists and also campaigned for the rights of prisoners during the war. He accepted the position of a chief physician for the prison camps. This was the first and last clinical position he held during his life [5]. Tigerstedt wrote a critical report on the camp conditions. However, in 1934, no mention was made about his contribution to humanity in the


Handbuch
der
physiologischen Methodik
Unter Mitwirkung
von
L. Asher, Bern; A. Bethe, Strassburg; Chr. Bohr, Kopenhagen; K. Bürker, Tübingen; W. Caspari, Berlin; J. R. Ewald, Strassburg; O. Fischer, Leipzig; O. Frank, München; M. von Frey, Würzburg; S. Garten, Giessen; A. Gullstrand, Upsala; F. B. Hofmann, Innsbruck; R. Magnus, Utrecht; L. Michaëlis, Berlin; W. Nagel, Rostock; C. Oppenheimer, Berlin; I. P. Pawlow, St. Petersburg; J. Poirot, Helsingfors; A. Pütter, Göttingen; M. Rubner, Berlin; K. Schäfer, Berlin; F. Schenck, Marburg; J. Steiner, Köln; W. Trendelenburg, Freiburg i. B.; W. Wirth, Leipzig; N. Zuntz, Berlin und H. Zwaardemaker, Utrecht
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Mit 92 Figuren
Leipzig
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1910

Fig. 4. Cover page of Tigerstedt's Handbook on methods in physiology "Handbuch der Physiologischen Methodik".

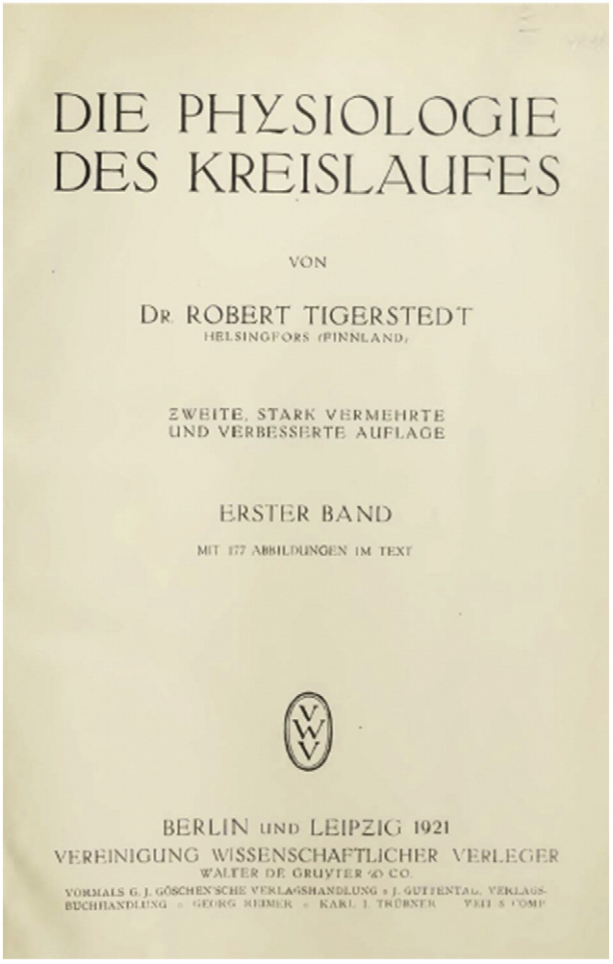
DIE PHYSIOLOGIE
DES KREISLAUFES
VON
DR. ROBERT TIGERSTEDT
HELSINGFORS (FINNLAND)
ZWEITE, STARK VERMEHRTE
UND VERBESSERTE AUFLAGE
ERSTER BAND
MIT 177 ABBILDUNGEN IM TEXT
BERLIN UND LEIPZIG 1921
VEREINIGUNG WISSENSCHAFTLICHER VERLEGER
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Fig. 5. Cover page of Tigerstedt's textbook on physiology of the blood circulation, "Die Physiologie des Kreislaufes", which fetched a Nobel Nomination for him in 1923.

Finnish biographical publication on him named, *Kansallinen elämäkerrasto* [38].

He was a prolific writer. He wrote extensively in various magazines, papers, and published pamplets and books. Drinking habits in Scandinavia were rampant then. Tigerstedt worked towards a strong antiliquor program [5]. He was appointed as a member to the State Alcohol Committee in 1922. His essay on alcoholism was very famous. More than 200,000 copies of "Om spirit dryckernas inverkan påkroppens normala förrättningar" (Finnish — Spirits impact on regular activities of the body) were issued between 1888 and 1891. He has also published many comprehensive works on scientists like Harvey, Vesalius, Lavoisier, Helmholtz, Ludwig [39]. He also wrote 'The brain as the organ of thought' (1889), 'Principles of food distribution in public institutions' (1891) and 'lectures in health education' (1895) [3].

Tigerstedt developed extensive reports on reorganization of medical education (1902 to 1911). He was instrumental in instituting new teaching methods and modernizing medical training in both Stockholm and Helsinki. Tigerstedt had the unique ability to get students interested in scientific research. He guided about 30 doctoral students. Tigerstedt is said to have had a huge collection of books in his library at the Department of Physiology, Helsinki. Unfortunately, the collection was destroyed by fire in 1923 [5].

Robert A.A. Tigerstedt died during sleep, at the age of 70 in Helsinki on 12th of February 1923. None of the then European Journals made a mention about renin in the obituaries published. Tigerstedt's son Carl (1882–1930) succeeded him as a Professor of Physiology.

It is said that Robert Tigerstedt would have been famous even if he had not discovered renin. He was the one who established a new, well equipped laboratory at Stockholm, the part of the world which lacked a physiology lab before this. According to one of his students, "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" [2].

Robert Tigerstedt can justly be said to have made an indelible imprint on the sands of science by his discovery of *Renin*.

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