**Historical Perspective**

**History About the Discovery of the Renin-Angiotensin System**

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**Abstract**—The history of the discovery of the renin-angiotensin system began in 1898 with the studies made by Tigerstedt and Bergman, who reported the pressor effect of renal extracts; they named the renal substance renin based on its origin. In 1934, Harry Goldblatt induced experimental hypertension in dogs by clamping a renal artery. About 1936, simultaneously in the Medical School of the University of Buenos Aires, Argentina, and in the Eli-Lilly Laboratories in Indianapolis, 2 independent groups of researchers, using the Goldblatt technique to produce experimental hypertension, demonstrated renal secretion of a pressor agent similar to renin. In the following years, both teams described the presence of a new compound in the renal vein blood of ischemic kidneys. This agent was extracted from blood with 70% acetone and had a short pressor effect. The final conclusion was that renin acted enzymatically on a plasma protein to produce the new substance. In Buenos Aires, it was called hypertensin; in the United States, angiotonin. In 1958, Eduardo Braun Menéndez from Argentina and Irving H. Page from the United States agreed to name it angiotensin. *(Hypertension. 2001;38:1246-1249.)*

**Key Words:** renin ■ angiotonin ■ angiotensin ■ renin substrate ■ renin activator

The first observation linking renal disease to left ventricle hypertrophy was reported by Richard Bright in 1836.¹ He related hypertrophy to an increased resistance to blood flow in the small vessels due to the altered condition of the blood. In 1868, George Johnson,² reporting studies on nephritis, suggested that hyaline-fibroid alterations in the renal vessels were due to an impure condition of the blood, which was also responsible for left ventricular hypertrophy. F.A. Mahomed,³ using a primitive sphygmograph for the first time, described high blood pressure in 1872. He also linked left ventricular hypertrophy to hypertension due to nephritis and reported the presence of high blood pressure in patients without renal disease.⁴,⁵ Finally, Riva-Rocci,⁶ in 1896, described the first indirect sphygmomanometer to measure arterial pressure in humans, and in 1905, Korotkoff⁷ defined the sounds that are named after him.

The relationship between pathological alterations in the kidney and the development of systemic arterial hypertension had been postulated for many years. In this sense, Franz Volhard⁸ suggested the existence of a circulating vasopressor substance. He classified the hypertensive patients: those with slight vascular damage as reds, and those with important vascular lesions—mostly in the kidney, pale skin, and cerebral damage (malignant hypertension)—as white.

On the other hand, by the end of the nineteenth century, Tigerstedt, a Finnish professor of physiology working at the Karolinska Institute, and his assistant Bergman⁹ analyzed the effect of renal extracts on arterial pressure. They discovered the presence of a pressor compound in the renal tissue of the rabbit, and based on its origin, they named it renin. The pressor activity could be extracted with glycerin, did not dialyze, and was stable at 56°C and was destroyed by boiling. Moreover, they showed that the renal vein blood increased blood pressure when injected into nephrectomized animals. They also detected the potentiation and protraction of the pressor response to renin in the nephrectomized recipient. They explained that the association between renal disease and cardiac hypertrophy was due to the kidney release of a vasoactive substance that induced contraction of the blood vessels through a direct action.

Based on these facts, many attempts were performed to develop an experimental model of arterial hypertension by manipulation of the renal function. Reduction of the renal mass, X irradiation of the kidney, renal artery occlusion, renal vein constriction, and wrapping of the kidney with a membrane were tested. Results were unreliable, probably as a consequence of inappropriate techniques and/or inadequate methods to measure blood pressure. The first successful experiment was performed by Goldblatt et al in 1934,¹⁰ and their technique led to the discovery of the active polypeptide. These researchers linked the ischemic characteristic of the renal disease with hypertension. They induced the experimental hypertension in the dog by the partial constriction of the renal artery using a silver clip. Their results were confirmed by several groups,¹¹ and the search for the mechanisms involved for the increase in blood pressure began. The section...
of the sympathetic nervous system that regulates the vaso-
motor mechanisms did not prevent or abolish the develop-
ment of hypertension.

Goldblatt had already proposed the existence of a humoral
mechanism due to the release of a pressor substance by the
kidney, even though he recognized that this possibility was
only sustained by indirect evidences. This concept was not
new, Volhard had suggested the presence of a vasoconstrictor
factor causing malignant, or "pale," hypertension. Nonethe-
less, neither he nor his collaborators could establish the nature
of such an agent in the circulation of patients suffering from
this pathology. Lack of its detection was probably due to
inadequate methods for analysis.

Two research groups, working independently, simulta-
aneously reached similar conclusions on this matter. One of
them was investigating at the University of Buenos Aires,
Argentina, under the leadership of Dr Bernardo Houssay at
the Physiology Institute of the School of Medicine. The other
group pursued their studies at the Eli Lilly Research Labora-
tories in Indianapolis, under the leadership of Dr Irvine H.
Page.

The discovery of the renin-angiotensin system in Buenos
Aires began with the arrival of Dr Juan C. Fasciolo, a young
physician, at the Institute chaired by Dr Houssay. He was
interested in performing his doctoral thesis in physiology
under the direction of Prof Houssay. The subject, selected by
Houssay, was to repeat the experiment described by Goldblatt
in the dog to find out the nature of the mechanisms involved
in the development of high blood pressure. The interest of Dr
Houssay in this problem was related to the fact that one of his
young disciples, 32-year-old Dr J. Guglielmetti, had recently
died of malignant hypertension.

They faced all kind of problems, but finally the develop-
ment of an adequate silver clip resulted in a number of
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studying renal grafts from hypertensive dogs and also when injecting blood coming from acute ischemic kidneys. Previous observations, therefore, linked renin with the newly discovered agent. However, the nature of the relationship between the 2 compounds remained unknown.

The first studies designed to clarify this matter were unsuccessful. Kidney slices were incubated with plasma (under hypoxic conditions). The release of the active principle could not be detected, probably because of the enzymatic destruction of the formed hypertensin. Then, they incubated a semipurified kidney extract with plasma and were able to isolate a vasoconstrictor substance similar to hypertensin. The compound was soluble in 75% acetone and in glacial acetic acid, was insoluble in ether and amyl alcohol, and was resistant to acid hydrolysis and dialyzable. These characteristics were different from those of renin, epinephrine, tyramine, vasopressin, and urohypertensin.

Based on these results, the Argentine group described, for the first time, renin as an enzyme similar to papain (protease), which could act on a protein present in the plasma to release hypertensin as the final product of the enzymatic reaction. Through subsequent experiments, these researchers demonstrated that renin was secreted by the kidney, and hypertensin was formed in the plasma from a proteic substrate that was named hypertensinogen because it was the actual origin of the active principle. Blood, as well as kidney, was able to inactivate hypertensin through the action of other enzymes that were called hypertensinases. Inactivation of hypertensin was avoided by purifying preparations containing either renin or hypertensinogen.

The fact that bilateral nephrectomy increased considerably the plasma concentration of hypertensinogen was also demonstrated. At the same time, the specificity of the enzymatic system was described. Hog renin could not release hypertensin from the human plasma substrate, whereas human renin was able to hydrolyze hog and cow hypertensinogen.

The hepatic origin of renin substrate was suggested by Page et al. However, conclusive experiments were performed later by Leloir et al in nephrectomized dogs with and without hepatectomy.

All the research performed on the renin-angiotensin system by the Argentine group were published in a book in 1943. Simultaneously, Page, working with Helmer and Kohlstaedt, was investigating the mechanism of action of renin. They had observed that when the purified protein was injected in the dog isolated tail preparation and perfused with Ringer solution, it was barely active compared with the strong constrictor and pressor effect obtained after intravenous injection. They postulated the existence of a blood component that was necessary for the vasoactive action of renin. They had observed that the addition of small amounts of plasma to the Ringer’s solution containing purified renin induced a strong vasoconstrictor effect in the perfused dog tail preparation. They concluded that renin was an inactive enzyme that was activated by yet another enzyme, belonging to the kinase group, that was present in the proteic fraction of plasma and blood. Therefore, this plasma protein compound was named renin activator. The final product, a pressor substance formed through the interaction of renin and its activator, was named angiotensin and was, probably, the actual effector of the renin pressor action.

The similarity between renin substrate and renin activator was immediately accepted, as was the identity of the final product. Moreover, the enzymatic nature of the renin system and the peptidic nature of the hypertensin was also confirmed. Renin acted as a hormone and as an enzyme with a pressor effect that was due to angiotensin release. Shortly after, Page et al changed the name of renin activator to renin substrate to emphasize the enzymatic nature of the system. During the following years, both nomenclatures were used, generating a certain degree of confusion.

Synthesis of the octapeptide was successfully accomplished, for the first time, by the group led by Dr Page, then in Cleveland, and by Dr Schwyzer in Basel, Switzerland. The Basil group, working at the CIBA laboratories, marketed the octapeptide under the name Hypertensin. To commemorate the 25-year anniversary of Goldblatt’s first successful experiment to induce arterial hypertension by renal ischemia in the dog, the University of Michigan Regional Conference on the Basic Mechanisms of Arterial Hypertension was held in Ann Arbor, Mich, in 1957 under the Organizing Committee of Drs Sibley W. Hoober and David F. Bohr. (Under the direction of these 2 distinguished investigators, several Argentine physicians were trained.) Back in Argentina, they continued to work on the mechanisms of arterial hypertension and on the renin-angiotensin system. Among them were Dr. Alberto Agrest, Pedro C. Blaquier, Alberto C. Taquini, Jr, and Ignacio J. de la Riva. All returned to work at the Instituto de Investigaciones Cardiológicas of the School of Medicine of the University of Buenos Aires, where they had begun their research studies. Dr Braun Menéndez et al and Dr Alberto C. Taquini et al presented their experimental results at the University of Michigan conference, and the results were published in a supplement to Circulation. Also at this meeting, Dr Braun Menéndez (for the Argentine team) and Dr Page (for the American group) arrived at a single nomenclature for the components of the enzymatic system. Even though there was already a marketed name of Hypertensin, Braun Menéndez agreed to name the active final compound angiotensin, taking half of each original name. Similarly, the renin substrate was named hypertensinogen, and the enzymes that metabolize the peptide were termed hypertensinases.

A few years were needed for the general acceptance of the new nomenclature. The leading groups in the United States, like those of Goldblatt and Skegg, and in Europe continued using the Argentine name. In 1959, Dr Braun Menéndez died, and in 1961, Taquini et al insisted on the necessity of using the unified nomenclature.

Those involved in the discovery of the renin-angiotensin system probably did not imagine the importance and transcendent significance of their findings as well as the enormous flow of information added to the knowledge of the enzymatic system. In spite of the fact that >50 years have elapsed, the role of the full implications of the renin-angiotensin system on the development of renal arterial hypertensin has not been completely elucidated. Notwithstanding, there are no doubts about the beneficial effect of inhibition of...
the enzymatic system in a group of essential hypertensive patients. In this sense, drugs that are able to block the effect of angiotensin II have contributed to modify the evolution of arterial hypertension and to increase the lifespan of the hypertensive patients.

References