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A cornerstone in the history of hypertension: the seventieth anniversary of the discovery of angiotensin

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In 1939, two independent teams, in Buenos Aires and Indianapolis, identified the polypeptide angiotensin. In 1934, Goldblatt *et al*. demonstrated that partial occlusion of the renal arteries produces hypertension in dogs, and Houssay in 1936 predicted the presence of a humoral mechanism and, with Fasciolo, demonstrated that the ischemic kidneys released a pressor substance that increased the recipient's blood pressure. Later on, Taquini proved that the rise in blood pressure that follows the re-establishment of circulation in kidneys was also produced by a plasmatic substance from the venous blood of acute ischemic kidneys and it was called 'hypertensin'. Then, they proved that it was the result of an enzymatic reaction in which renin was the enzyme and plasma the substrate. At the same time, in 1939, Page *et al.* postulated that renin activated by plasma becomes vasoactive and the substance was called 'angiotonin'. Page's group began in 1937, with the purification of renin, studying its renal hemodynamic effects. Later on, Page *et al.* acknowledged in 1943 the enzymatic nature of the system and renamed their so-called renin-activator as renin substrate. Both groups fused the two original names into 'angiotensin' during a meeting at Michigan in 1958, making the 'adventure of the discovery of angiotensin' a reality. *J Cardiovasc Med* 11:260–264 © 2010 Italian Federation of Cardiology.

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Introduction

In 1939, two independent research teams, in Buenos Aires and Indianapolis, headed by Eduardo Braun Menéndez and Irving H. Page, respectively, identified the polypeptide angiotensin related to the pressor effect of renal hypertension [1].

The Argentine research group

At the end of 1943, due to political persecution against Bernardo Houssay, its mentor, that group was dissolved (Fig. 1). Because of the subsequent premature death in 1959 of Braun Menéndez, some twists in the tale of the discovery of angiotensin have remained ignored.

However, 'the Argentine adventure: the discovery of angiotensin' can be recreated on the basis of the review by Basso and Terragno [2] and recently, in 2005, by Milei and Alberto [3], and some unpublished articles, letters and documents.

The interest of the Argentine team in the field of hypertension began in 1931 during Taquini's visit to Volhard's laboratory as a member of the Houssay (Nobel Prize, 1947) group. Volhard was the first to postulate that vasospasms, characteristic of pale hypertension, were produced by a vasoconstrictor substance released by the kidney [4].

Two years thereafter, the classical report by Goldblatt *et al*. (Fig. 2) [5], showing that partial occlusion of the renal arteries produces sustained hypertension in dogs similar to that seen in humans, with some evidence denying its reflex origin [6], led Houssay, an endocrinophysiologist, to predict the presence of a humoral mechanism.

In 1936, he asked Fasciolo, an active medical graduate, to reproduce Goldblatt's technique. Then, with praiseworthy skill, Houssay with Fasciolo [7] demonstrated that the ischemic kidneys released a pressor substance that increased the recipient's blood pressure.

Taquini narrated the circumstances as follows [4]:

'At the time Houssay and Fasciolo performed their experiments, I was head of the Cardiovascular Laboratory of the Institute and, with Volhard's hypothesis in mind, I discussed with them the possibility that the pressor substance released by the ischemic kidney might act directly on the vessels. Houssay firmly supported this hypothesis and advised me to test it with the Löwen Trendelenburg technique, which I did with positive results. In fact, the plasma of blood leaving the clamped kidney proved to have a definite constrictor effect on the isolated vessels of the toad's legs…'.

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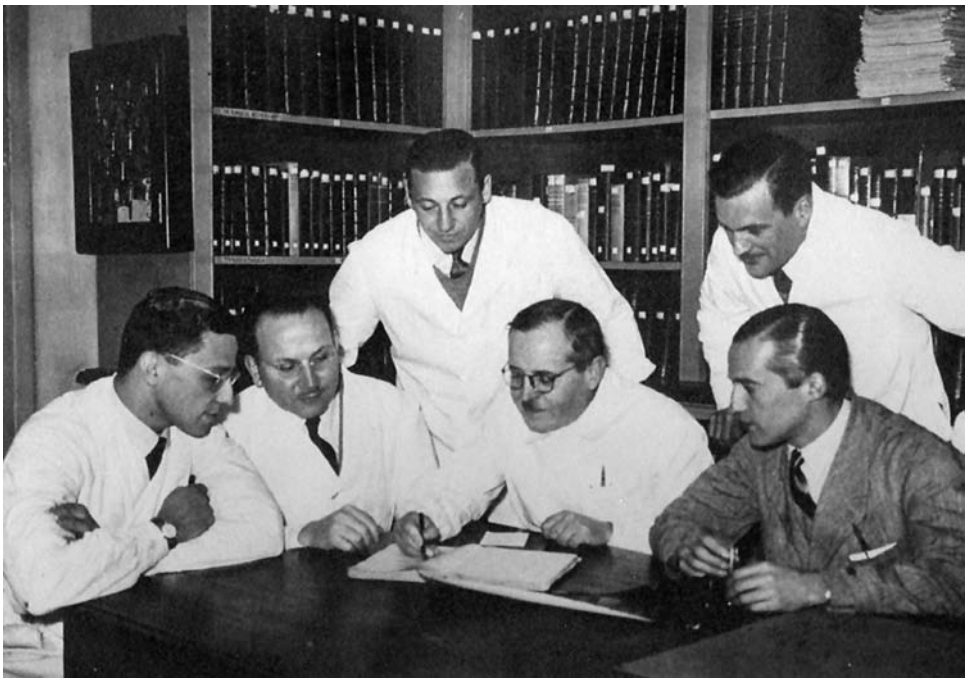
Fig. 1



The Argentine group. From left to right: Juan Carlos Fasciolo, Juan M. Muñoz, Alberto C. Taquini (standing), Bernardo A. Houssay (Nobel Prize 1947), Eduardo Braun-Menéndez (standing), Luis F. Leloir (Nobel Prize 1970).

Houssay's, Fasciolo's and Taquini's experiments led them to affirm that Goldblatt's hypertension was the result of a vasoactive substance released by the ischemic kidney [8].

Later on, Taquini [9] proved that the rise in blood pressure that follows the re-establishment of circulation in kidneys was also produced by the release of the same vasoactive substance. Afterwards, Menéndez and Fasciolo [10] perfused isolated kidneys, using a heart–lung preparation, and showed that the kidney needs only to be ischemic for a short time to release the pressor substance.

In 1938, Houssay delegated the problem to a team formed by Braun Menéndez, Fasciolo, Leloir (Nobel Prize 1970), Muñoz and Taquini.

The first result was attained in 1939, while Taquini was in the United States working as research fellow at Harvard University. Braun Menéndez, Fasciolo, Leloir and Muñoz (working in Buenos Aires) extracted a pressor substance from the plasma of venous blood of acutely ischemic kidneys. The substance was dialyzable, thermostable and with a short pressor effect; they called it 'hypertensin' [11]. Soon after, they proved that it was the result of an enzymatic reaction in which renin was the enzyme and plasma the substrate [12].

By the end of 1938, Leloir and Muñoz had joined the group, in order to collaborate in the identification of the vasoactive substance, already detected [9]. A little afterwards Taquini went to Harvard, and Braun Menéndez, already returned from Cambridge, took his place in Buenos Aires.

At the same time, Page and coworkers [13] (Fig. 3) presented their communication 'Activation of renin and its vasoconstrictor properties' at the Meeting of the American Heart Association, held in May 1939. In it they postulated that renin activated by plasma becomes vasoactive.

Taquini was present at that meeting, to which he had been invited to present his experience with totally ischemic kidneys. Forty-two years later [4], in his 'Personal Memories', he narrated the discussion at the meeting: 'Well informed that the properties of the substance isolated by my peers clearly showed that it was not renin, I objected to Page's and coworkers interpretation. Goldblatt who was also present, apparently, was the only one to take my comments into consideration. At the end of the sessions he invited me to stop at his laboratory on my way back to Boston in order to analyze the problem more extensively...'

Taquini sent his presentation to the *American Heart Journal*. It was published on May 1940 [14]. In that article, it was concluded that

Fig. 2

Original portrait of Harry Goldblatt autographed 'To Dr Taquini with kindish regards'.

Fig. 3

Original portrait of Irving Page autographed 'To Dr Taquini with warm regards and respect'.

(1) the re-establishment of circulation to a totally ischemic kidney causes a rise in arterial pressure;
(2) this rise is caused by the liberation of a pressor substance formed during total renal ischemia;
(3) this substance acts directly upon the peripheral vessels and produces marked vasoconstriction and consequent hypertension.

To recapitulate, the description of renin as an enzyme acting on a plasmatic protein to form hypertensin (angiotensin) had been defended by Taquini at the Meeting mentioned and in the presence of the other fathers of hypertension on 12 May 1939 at St Louis, Missouri.

In the years that followed the discovery of angiotensin, the Argentine group studied its enzymatic release from angiotensinogen, the secretion of renin by the kidneys, identified angiotensin as a peptide and its formation by the liver [15]. As a final contribution, the group wrote the book *Hipertensión Arterial Nefrógena*, which was published in 1943 and translated into English [16]. But, because of the already mentioned political persecution against Houssay, the group was dissolved.

Braun Menéndez continued his work together with his mentor Houssay in the private Instituto de Biología y Medicina Experimental, awaiting quieter times. He eventually rose to professor of Physiology in the University of Buenos Aires in 1956. Most unfortunately, he died in 1959 in an airplane crash.

Taquini founded the Instituto de Investigaciones Cardiológicas in 1944 and directed it for more than 54 years, until his death in 1998. During his long and fruitful life, he received more than a 100 national and international awards, published more than 350 papers and formed a legion of disciples [17]. Fortunately, the manuscripts, letters and documents related to this report were kept for more than 60 years in one of the drawers of his desk. This valuable treasure was recovered by myself upon becoming the Director of the Institute [3].

Fasciolo (1911–1993) worked with Taquini until he became the Chair of Physiology at Cuyo University in Mendoza. He continued his research on hypertension until his death.

Leloir (1906–1987) was a Research Assistant in Carl F. Cori's laboratory in St Louis in 1944 and thereafter he returned to Argentina and worked on the metabolism of galactose, which led him to earn the Nobel Prize in Chemistry in 1970.

The American research group

In his seminal book, Page related the facts as follows [18]: '...our work on the purification of renin began again in 1937, with Helmer doing the fractionation, Corcoran studying the renal hemodynamic effects, and Kohlstaedt measuring the vasoconstriction in dog's tail perfused with Ringer's solution, a method that was compared with the perfused isolated rabbit's ear vessels by a technician. I tested the samples in intact dogs and cats and also after various organs had been removed. In a sense it was this fortuitous arrangement that led to the discovery of angiotensin. It became apparent that as the fractionation of the kidney extract progressed, the pressor action in intact animals was becoming greater, but in the rabbit ear vessels and the dog's tail perfused with Ringer's solution, constriction was growing weaker'.

At that time, a sample of renin was left on Page's desk for several days. When he tested it, a surprising sharp increase in arterial pressure over 300 mmHg was observed. The curve of blood pressure rise was instantaneous and not very similar to that of renin. These two findings led them to affirm that a new substance had been formed and that an enzymatic reaction was involved. By perfusing the dog's tail or rabbit's ear with plasma and injecting renin, Page and coworkers were able to demonstrate a sharp increase in vasoconstriction as the purification advanced [18].

However, there were some detours in the route of the American group. In early 1938, they reported 'the activation of renin by blood colloids'. Page has explained the circumstances: 'In retrospect, we were sorry we used the term 'activation'. It was done out of extreme caution to avoid suggesting something unproved. We hoped it indicated that renin was an enzyme that in itself had no vascular activity. We said, 'If renin is an enzyme, then it seems reasonable to suppose the activator is the substance on which it acts'. We were roundly criticized for our caution. The problem was carried further in a detailed study published in November 1939 on the nature of the action of renin [19], in which the pressor activity of renin was shown to be dependent of the presence of renin 'activator' or 'substrate' [18].

As a consequence, the active agent received the name of 'angiotonin' and the full-length article 'On the nature of the pressor action of renin' was published in 1939 [20] and in the *American Heart Journal* [13] because of having been presented on 13 May, at the Meeting of the American Heart Association.

Later on, Page *et al.* [21] acknowledged in 1943 the enzymatic nature of the system and renamed their so-called renin-activator as renin substrate.

However, the announcement of the discovery of angiotensin created almost no interest. Many investigators doubted its existence, Harry Goldblatt among them [18] in spite of the attention he paid to it during the meeting of 1939. Furthermore, in his 'Introductory lecture on the production and pathogenesis of experimental hypertension' at a meeting in June 1946, hypertensin-angiotonin was/were ignored and the Argentine group bibliography dismissed [22]. We did not find any explanation for this, except for his final words: '...the nature of the humoral mechanism of experimental renal hypertension... will be discussed by the other participants in this Conference' (?).

Linguistic resolution: angiotensin

Both groups were concerned about the duality 'hypertensin-angiotonin' and agreed to fuse the two original names into 'angiotensin'. During an interview taped by Frohlich [1], Page pointed out '...that while enjoying martinis with Braun Menendez at the University of Michigan meeting we arrived at a compromise nomenclature for angiotonin-hypertensin: angiotensin as published in *Science* in 1958' [23]. This was emphasized in a letter to Fasciolo in June 1985 [24]: 'Too bad we can't leave a historical puzzle so some youngster can write a book about a controversy which did not occur. I hope the hypertensin story can be a model for future scientists to show how difficult situations can be solved like gentlemen and friends'.

Afterwards, with the passing of time, the 'adventure of the discovery of angiotensin' was no longer an adventure as an overwhelming body of evidence made angiotensin a reality.

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