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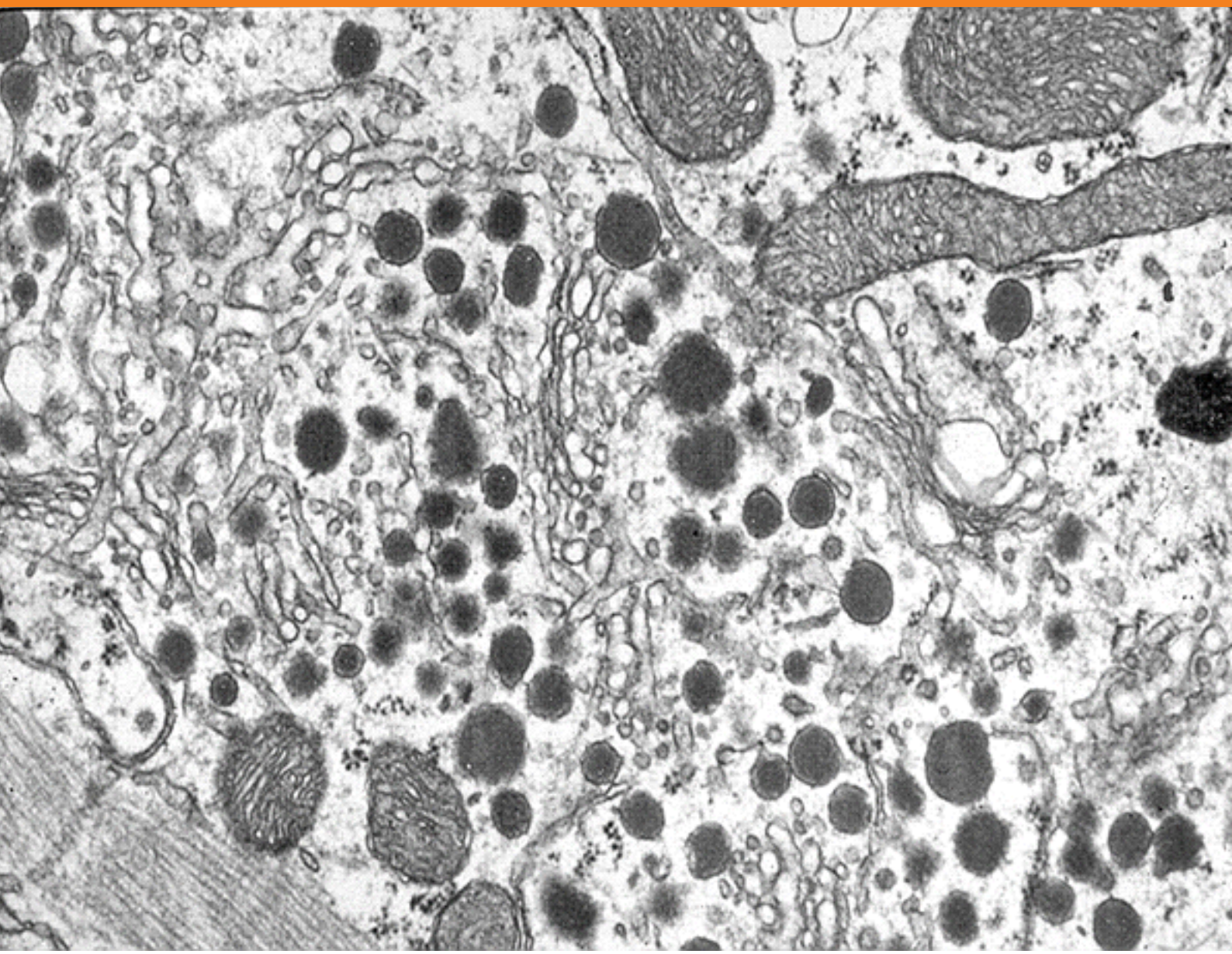

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The discovery of Angiotensin: a foundational step in the history of hypertension

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THE DISCOVERY OF ANGIOTENSIN: A FOUNDATIONAL STEP IN THE HISTORY OF HYPERTENSION

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ABSTRACT

More than 80 years ago, in 1939 two independent teams in Buenos Aires and Indianapolis, headed by Eduardo Braun Menendez and Irving H. Page, identified the polypeptide angiotensin related to the pressor effect of renal hypertension.

The interest of the argentine team in hypertension began in 1931 during Taquini's visit to Volhard´s laboratory as a member of the Houssay (Nobel Prize, 1947) group (the other members were Braun Menéndez, Fasciolo, Leloir (Nobel Prize 1970) and Muñoz). Two years thereafter, Goldblatt´s demostrated 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. Later on, Taquini proved that the rise in blood pressure which follows the re-establishment of circulation in kidneys was also produced by the release of a substance: "hypertensin (from the plasma of venous blood of acute ischemic kidneys). Soon after, 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 May 1939 Page et al postulated that renin activated by plasma becomes vasoactive ("angiotonin").

Page and his group (Kenneth, Kohlstaedt, Helmer and Corcoran) began in 1937, with the purification of renin, studying its renal hemodynamic effects and measuring the vasoconstriction in dog´s tail perfused with Ringer´s solution. Because of a fortuitous arrangement, a sample of renin was left on Page´s desk for several days. When he finally tested it, a surprising sharp increase in arterial pressure was observed. Later on, Page et al acknowledged in 1943 the enzymatic nature of the system and both groups agreed to fuse the two original names into "angiotensin".

Keywords: angiotensin, hypertension, renin-angiotensin system, blood pressure, kidney ischemia. (angiotensia, hipertensión, sistema renina-angiotensina, isquemia renal)

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As emphasized in the review by Basso and Terragno [1], in their tribute to the 'Sixtieth Anniversary of Angiotensin' [2], and 'In Memoriam' by Basso and Schiffrin [3], the discovery of angiotensin was a cornerstone in the history of hypertension [4-9].

In effect, on the basis of Taquini's autobiographical notes [10, 11] and some unpublished documents found by myself at the time of taking charge as the Director of the Instituto de Investigaciones Cardiológicas 'Prof. Dr. Alberto C. Taquini', I will attempt to make known some ignored aspects of the 'links' that led to the discovery of angiotensin [4]. Notably, the manuscripts, letters and documents related to this report had been kept in one of the drawers of Taquini's desk as a valuable treasure.

In 1939, two independent research teams in Buenos Aires and Indianapolis, headed by Eduardo Braun Menendez 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 (Figure 1)

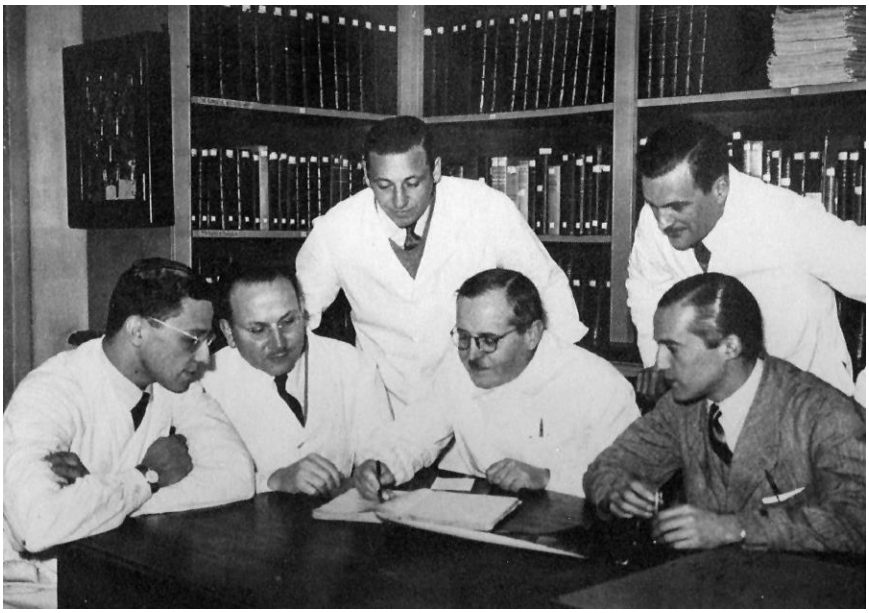


Figure 1. The Argentine group. From left to right: Juan Carlos Fasciolo, Juan M. Muñoz, Alberto C. Taquini (standing), Bernardo A. Houssay (Nobel Prize 1947), Eduardo Braun Menendez (standing), Luis F. Leloir (Nobel Prize 1970).

Because of the subsequent premature death in 1959 of Braun Menéndez, unfortunately some twists in the tale of the discovery of angiotensin have remained ignored.

The interest of the argentine team in the field of hypertension began in 1931 during Taquini's visit to Franz Volhard´s laboratory as a member of the Houssay (Nobel Prize, 1947) research group. Volhard was the first to postulate that vasospasms, characteristic of pale hypertension, were produced by a vasoconstrictor substance released by the kidney [1].

Two years thereafter, Goldblatt´s classical report showing that partial occlusion of the arteries produces sustained hypertension in dogs similar to that seen in human beings [12], plus some additional evidence denying its reflex origin [13], led Houssay, to predict the presence of a humoral mechanism.

In 1936, he asked Fasciolo, an active young medical graduate, to reproduce Goldblatt´s technique. Houssay with Fasciolo [14] were able to demonstrate that the ischemic kidneys released a pressor substance that increased the recipient´s blood pressure. Taquini narrated the circumstances as follows [11]:

"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 [15]…". As a consequence, those experiments led them to affirm that Goldblatt´s hypertension was the result of a pressor vasoactive substance released by the ischemic kidney [16].

Later on, using the same methods, Taquini proved that the rise in blood pressure which follows the re-establishment of circulation in kidneys was also produced by the release of the same vasopressor vasoactive substance [17].

Afterwards, Fasciolo and Braun Menéndez perfused isolated kidneys, using a heart lung preparation, and showed that the kidney must only be ischemic during a short time to release the vasoactive substance [18].

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

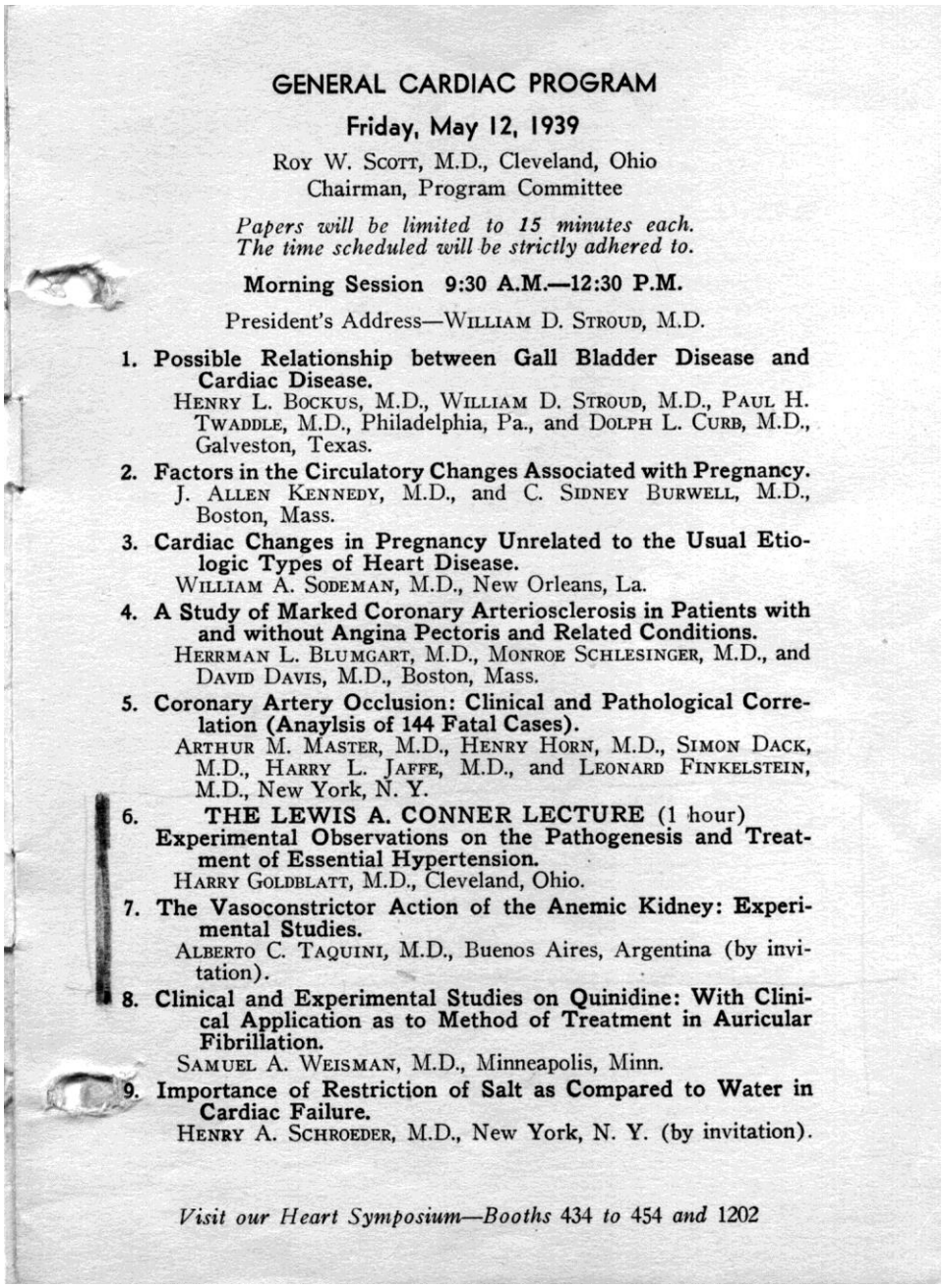
The first noteworthy result was attained in 1939. At that time, Taquini and Braun Menéndez crossed their paths; Taquini began his fellowship in Harvard, and Braun Menéndez, returned from Cambridge, and returned his position in Buenos Aires. Braun Menéndez, Fasciolo, Leloir and Muñoz at the Institute of Physiology, extracted a pressor substance from the plasma of venous blood of acute ischemic kidneys. The substance was dializable, thermostable and with a short pressor effect; they called it "hypertensin" [19]. Soon after they proved that it was the result of an enzymatic reaction in which renin was the enzyme and plasma the substrate [20].

By the end of 1938, Leloir and Muñoz joined the group following a suggestion by Houssay, in order to collaborate in the identification of the vasoactive substance, already detected [19,20].

At the same, Irving Page (Figure 2) with G. Kenneth, K.G. Kohlstaedt and O.M. Helmer, presented their communication "Activation of renin and its vasoconstrictor properties" at the Meeting of the American Heart Association, held in May 1939, where they postulated that renin activated by plasma becomes vasoactive [21].

Figure 2. Original portrait of Irving Page autographed "To Dr. Taquini with warm regards and respect".

Taquini was present at that meeting, to which he had been invited to present his experience with totally ischemic kidneys (Figure 3).



GENERAL CARDIAC PROGRAM

Friday, May 12, 1939

Roy W. Scott, M.D., Cleveland, Ohio
Chairman, Program Committee

Papers will be limited to 15 minutes each.
The time scheduled will be strictly adhered to.

Morning Session 9:30 A.M.—12:30 P.M.

President's Address—William D. Stroud, M.D.

1. **Possible Relationship between Gall Bladder Disease and Cardiac Disease.**
   Henry L. Bockus, M.D., William D. Stroud, M.D., Paul H. Twaddle, M.D., Philadelphia, Pa., and Dolph L. Curb, M.D., Galveston, Texas.
2. **Factors in the Circulatory Changes Associated with Pregnancy.**
   J. Allen Kennedy, M.D., and C. Sidney Burwell, M.D., Boston, Mass.
3. **Cardiac Changes in Pregnancy Unrelated to the Usual Etiologic Types of Heart Disease.**
   William A. Sodeman, M.D., New Orleans, La.
4. **A Study of Marked Coronary Arteriosclerosis in Patients with and without Angina Pectoris and Related Conditions.**
   Herrman L. Blumgart, M.D., Monroe Schlesinger, M.D., and David Davis, M.D., Boston, Mass.
5. **Coronary Artery Occlusion: Clinical and Pathological Correlation (Anaylsis of 144 Fatal Cases).**
   Arthur M. Master, M.D., Henry Horn, M.D., Simon Dack, M.D., Harry L. Jaffe, M.D., and Leonard Finkelstein, M.D., New York, N. Y.
6. **THE LEWIS A. CONNER LECTURE** (1 hour)
   Experimental Observations on the Pathogenesis and Treatment of Essential Hypertension.
   Harry Goldblatt, M.D., Cleveland, Ohio.
7. **The Vasoconstrictor Action of the Anemic Kidney: Experimental Studies.**
   Alberto C. Taquini, M.D., Buenos Aires, Argentina (by invitation).
8. **Clinical and Experimental Studies on Quinidine: With Clinical Application as to Method of Treatment in Auricular Fibrillation.**
   Samuel A. Weisman, M.D., Minneapolis, Minn.
9. **Importance of Restriction of Salt as Compared to Water in Cardiac Failure.**
   Henry A. Schroeder, M.D., New York, N. Y. (by invitation).

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Figure 3. Original program of the Scientific Sessions of the American Heart Association of 1939. A fragment of the original program where Taquini marked Goldblatt's and his own presentation.

Fortytwo years later [11], in his "Personal Memories", he narrated the discussion that developed 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 immediately his presentation to the American Heart Journal. It was published on May, 1940 [22]. In that paper it was concluded that:

The re-establishment of circulation to a totally ischemic kidney causes a rise in arterial pressure, by the liberation of a pressor substance formed during total renal ischemia.
This substance acts directly upon the peripheral vessels and produces marked vasoconstriction and consequent hypertension.
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 studied the formation of angiotensinogen by the liver, [23-25]. As a final contribution, the group wrote the book Hipertension Arterial Nefrógena, which was published in 1943 and translated into English [26]. At the end of that year, and 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 a commercial 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 hundred national and international awards, published more than 350 papers in high level journals, and formed a legion of disciples [24]. 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 this author upon becoming the Director of the Institute [6].
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 for his discovery of sugar nucleotides and their role in the biosynthesis of carbohydrates.

The American Research group

In his seminal book, Page related the facts as follows [27]: "…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 finally tested it, a surprising sharp increase in arterial pressure over 300 mm Hg 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 into it, Page

and co-workers were able to demonstrate a sharp increase in vasoconstriction as the purification advanced [28].

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, in which the pressor activity of renin was shown to be dependent of the presence of renin 'activator' or 'substrate' " [27].

As a consequence, the active agent received the suggestive name of "angiotonin" and the full-length paper "On the Nature of the Pressor Action of Renin", was published in 1939 in The Journal of Experimental Medicine [29] and in the American Heart Journal because of having been presented on May 13, at the Meeting of the American Heart Association.

Later on, Page et al [30] 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 [31] 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" delivered at a Meeting in June 1946, hypertensin-angiotonin was/were ignored and the Argentine group bibliography dismissed. 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 [2], Page pointed out "…that while enjoying martinis with Braun Menendez (Figure 6) at the University of Michigan meeting we arrived at a compromise nomenclature for angiotensin- hypertensin: angiotensin as published in Science in 1958 [32]. This was emphasized in a letter to Fasciolo in June 1985 [33]: "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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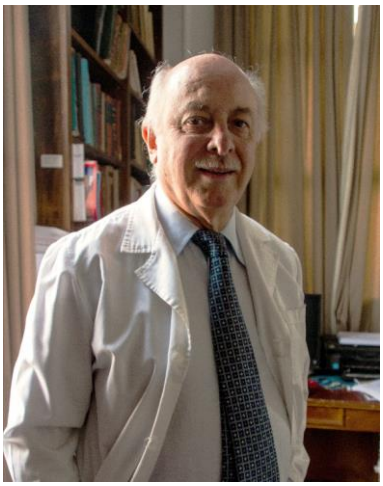
About authors



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Es Profesor Emérito de Medicina Interna de la Facultad de Medicina (UBA) y Miembro de la Carrera del Investigador del Conicet, categoría Superior.

Su tesis sobre los efectos de isoproterenol en el miocardio fue publicada en Am Heart J en 1976 y ha sido ampliamente citada internacionalmente. Fue becario en el Armed Forces Institute of Pathology, Walter Reed Hospital e investigador visitante en la década del '80 en el NIH, National Heart, Lung, and Blood Institute, USA, bajo la guía de su mentor, Víctor Ferrans.

Es Miembro Titular de la Sociedad Argentina de Cardiología desde el año 1975, ocupando diversos cargos societarios. Forma parte del Comité Editorial de varias revistas científicas nacionales e internacionales.

Sus investigaciones sobre la cardiomiopatía chagásica crónica contribuyeron al conocimiento de su fisiopatología y su tratado "Enfermedad de Chagas" continúa siendo el libro de referencia en los últimos 20 años.

Sus trabajos sobre las lesiones pre-ateroscleróticas en los fetos y niños ayudaron a sentar las bases de la importancia de los engrosamientos intimales en la génesis de la placa. Son conocidas sus investigaciones en infarto indoloro en el diabético, isquemia-reperfusión, hipertensión y sindrome metabólico.

Fue Subsecretario Académico y Consejero Académico de la Facultad de Medicina (2002-2008), UBA. Ha publicado más de 450 trabajos de investigación clínica o aplicada, 169 en revistas indizadas en Medline, así como más de una decena de libros. Ha desarrollado profundos lazos de cooperación científica con diversos centros de fama internacional.