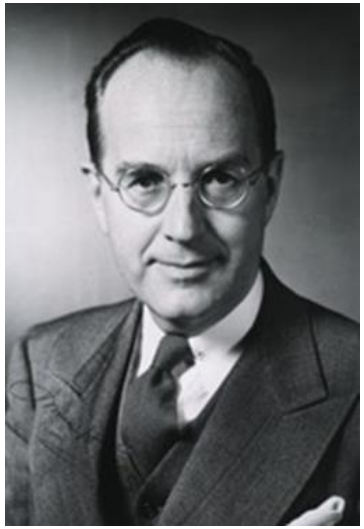
# La Saga del eje Renina-Angiotensina-Aldosterona: historia y perspectivas

.

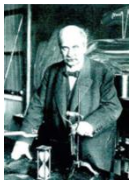
*Dr Hernan Valdés-Socin*
*Prof Adjunto. Fisiopatologia.Universidad de Lieja*
Miembro de la Sociedad Francesa de Historia de la Medicina
*Servicio de Endocrinología. CHU de Lieja*

Prof Dr Eduardo Braun Menéndez
(1903-1959)



Dr Irvine Page
(1901-1991)

# Hipertensión : hechos históricos



*Tigerstett*

*Loesch*

*Corneille Heymans*

*Harry Goldblatt*

*Braun Menéndez & Irving Page*

*Simpson & Tait*

*J Conn*

1898 1927 1930 1934 1939 1949 1953 1955 1956

Extractos de **rénina**

HTA inducida por isquemia renal

Seno aortico et regulacion PA

HTA inducida por isquemia renal

**Hypertensina/ Angiotonina**

Bradykinina

*Maricio Rocha e Silva*

**Electrocortina/ aldosterona**

Hyperaldosteronismo Primaire

Amphenone **/Espirinolactona**

***De**: Valdes-Socin et al. RmLg 2020*

# Hipertensión : hechos históricos (II)

*Sergio Ferreira (1934-2016)*

*Miguel Ondetti (1930-2004)*

*Adolfo de Bold & al (1942- 2021)*

*Skeggs & al*

*Corvol & Ménard*
*Murakami & Inagami*

*Sudoh et al*

*Kitamura et al*

1956 1965 1970 1977 1979 1981 1988 1993 2020

Isolation Angiotensine I et II

Venin *Bothrops Jaraca*

**Isolation ACE**

**Sintesis del captopril (Capoten® Squibb)**

Sintesis Renina

Atrial Natriuretic Peptide

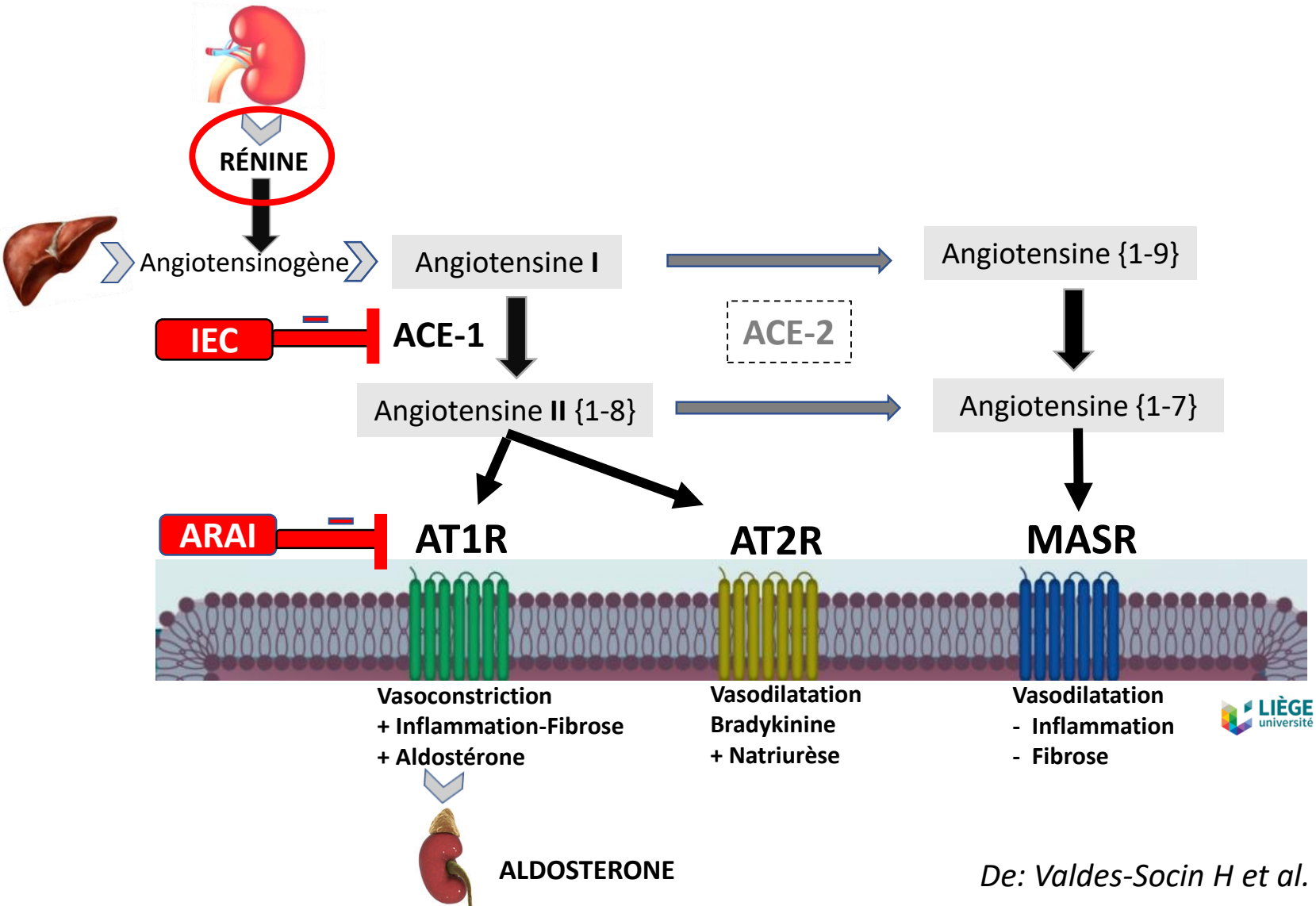
Brain Natriuretic Peptide

Adrenoméduline (hypotenseur)

**COVID 19**

***De**: Valdes-Socin et al. RmLg 2020*

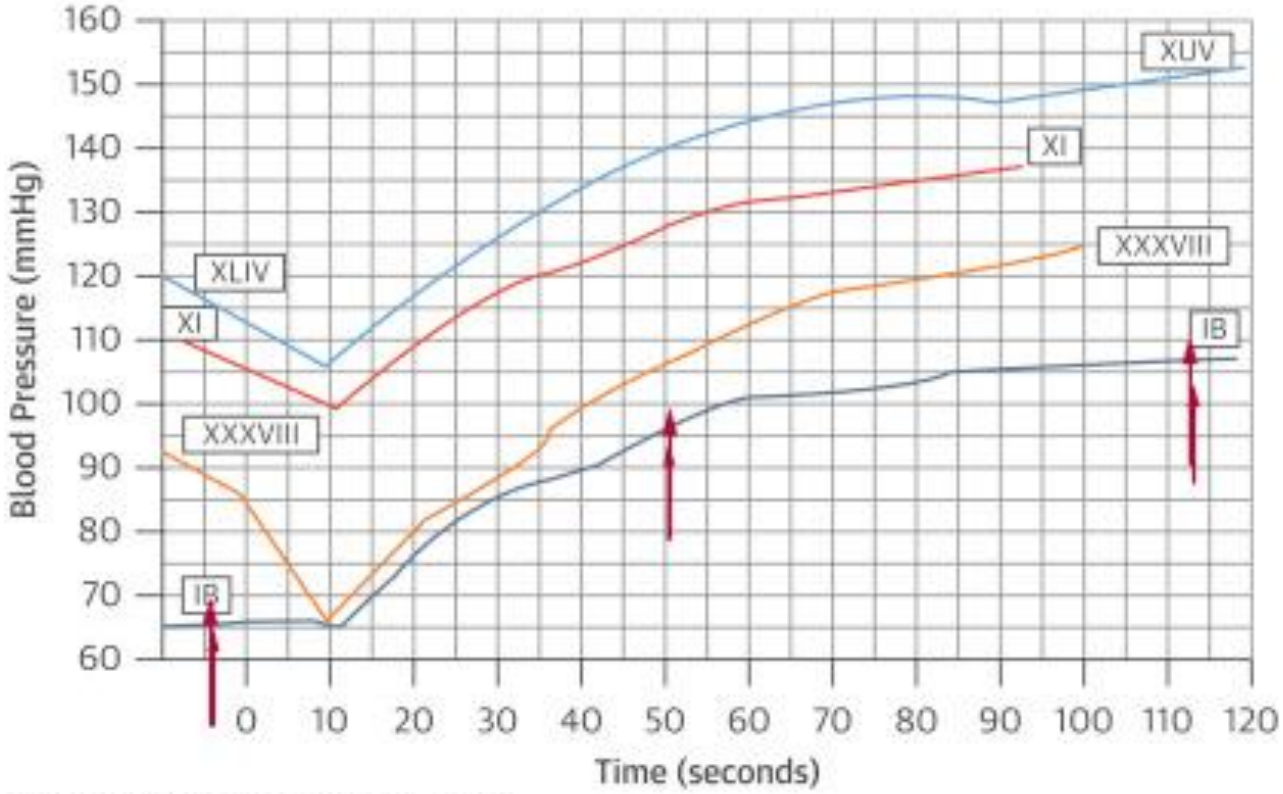
# Eje Renine-Angiotensina-Aldosterona



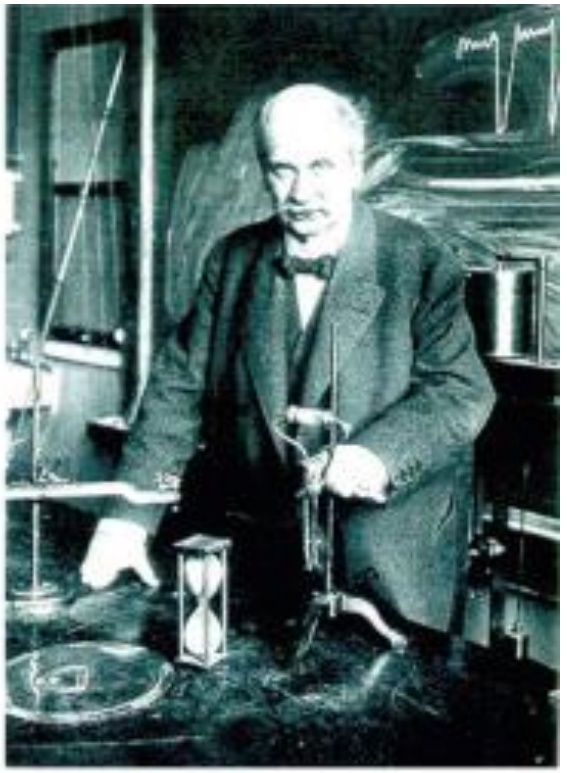

*De: Valdes-Socin H et al. RmLg 2020*

# Descubrimiento de la Renina

"A [rabbit] kidney was pulverized with 21 ml of water. Injection into jugular vein. Within 80 s, there is a rise in mean arterial pressure from 62-67 mmHg to 100 mmHg, i.e. an increase by ca. 50%."




Experiment 1B, November 8, 1896
Tigerstedt and Bergman, *Niere und Kreislauf*
Skand. Arch. Physiol. 8: 223-271, 1898



Robert Adolf Armand Tigerstedt (ca. 1910)

Karolinska Institute, Stockolm

***de**: E. Branwald. JACC 2015*

# Corneille Heymans (1892-1968)

## -Premio Nobel Medecina o Fisiologia 1938-

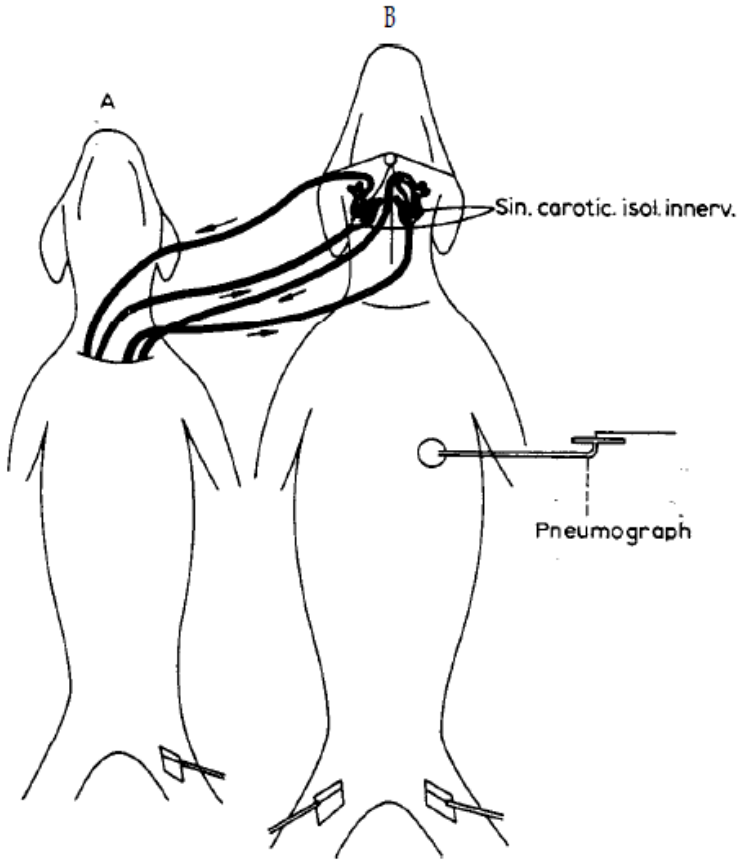
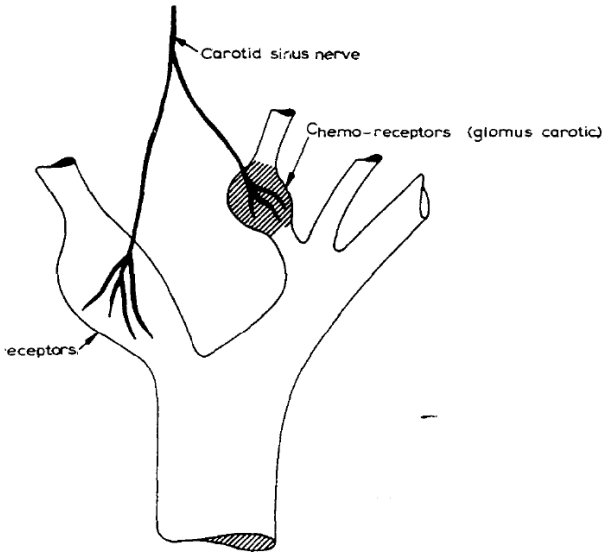



Fig. 10. Diagram of the procedure for perfusion of the carotid sinus with intact nervous connections and isolated circulation in Dog B from Dog A.



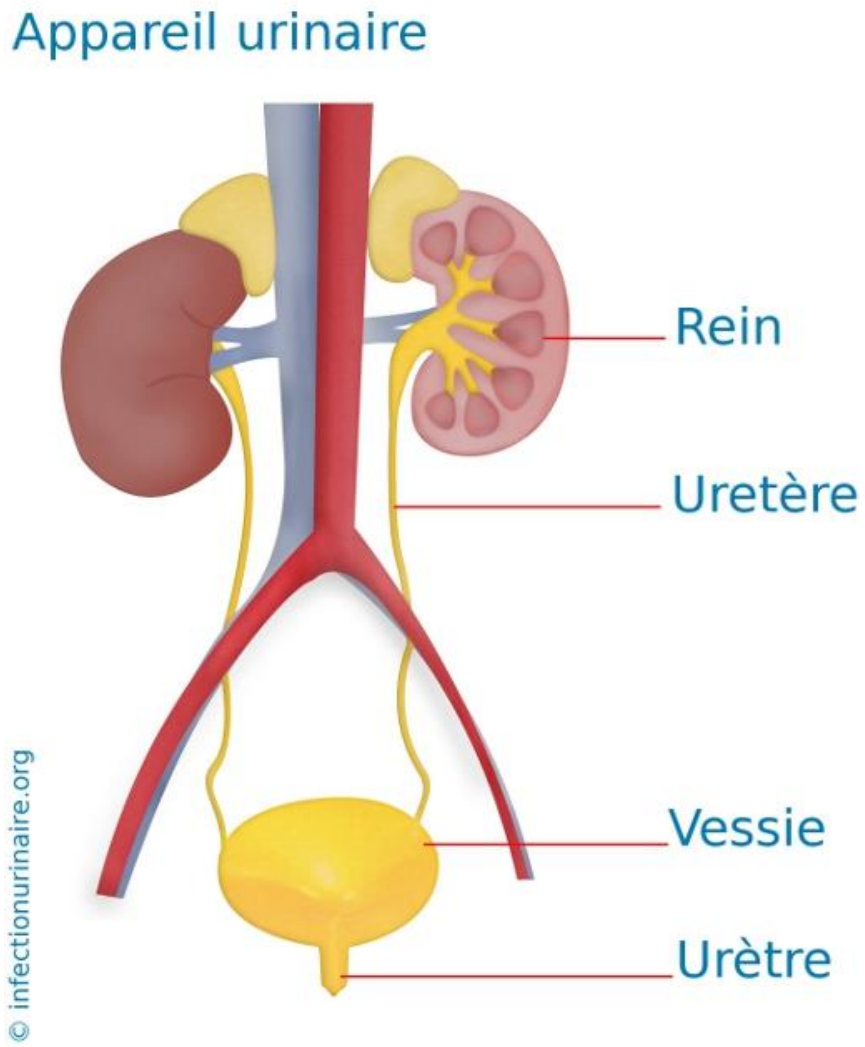



um showing the site of the reflexogenic presso- and chemo-receptors in the carotid sinus.

# Hipertensión Nefrógena

**Modelos de HTA**

- Irradiación renal
- Nefritis toxica
- Nefrectomía parcial (**Biasotti, 1927**)
- Estenosis de la vena renal
  (**Braun-Menéndez, 1933, Houssay & Taquini1938**)
- Estenosis art renal (**Goldblatt & al, 1934**)
- Efectos presores extracto riñón isquémico
  (**Harrison & al 1936, Prinzmetal et al 1936, Heymans C & Bouckaert 1938**)



# John Loesch (1897-1965)

- John Loesch (1897-1965) nació en Austria-Hungría. Emigró a los Estados Unidos en 1924.
- **En 1927,** publicó los resultados preliminares de sus investigaciones sobre la hipertensión de origen renal ya en 1927, induciendo isquemia renal en perros. Loesch dividió a sus animales en 2 grupos, animales de 1 riñón y animales de 2 riñones.
- Goldblatt, a diferencia de Loesch, no examinó el sedimento de orina.
- Sus obras originales, publicadas en alemán, permanecieron desconocidas durante mucho tiempo. Además, Loesch no hizo de la hipertensión su campo de investigación.

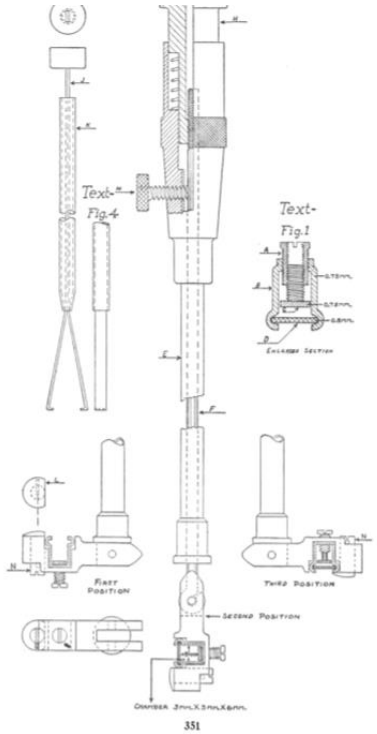
LOESCH J. - Further observations in experimental nephritis. Arch. Path., 1927,4, 495-496.
**Loesch J**. Ein Beitrag zur experimentellen Nephritis und zum arteriellen Hochdruck. III. Die Veränderungen in den Geweben. Zentralblatt für Innere Medizin. 1933;8:177-85.

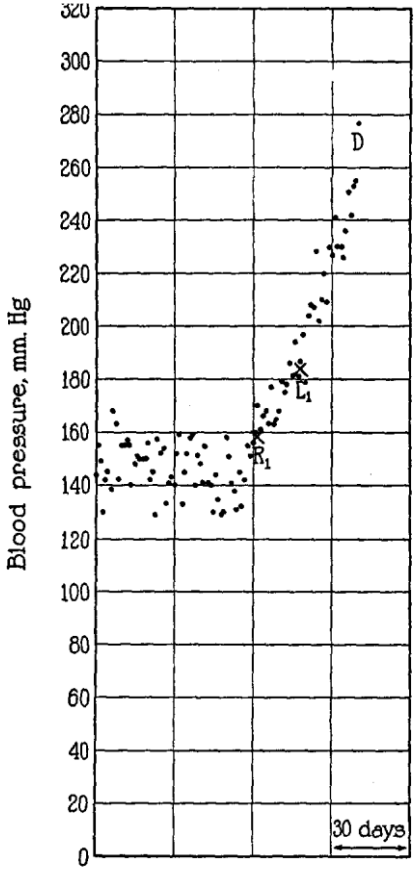
# STUDIES ON EXPERIMENTAL HYPERTENSION

## I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia*†

By HARRY GOLDBLATT, M.D., JAMES LYNCH, M.D., RAMON F. HANZAL, Ph.D., and WARD W. SUMMERVILLE, M.D.

*(From the Institute of Pathology, Western Reserve University, Cleveland)*




**1934**

# La Odisea de la Angiotensina


Instituto de Fisiología – UBA
Grupo de Braun Menéndez
***Hypertensina***


Laboratorios Eli Lilly-Indianapolis
Grupo de Irving Page
***Angiotonina***

# Hipertensión nefrógena y Angiotensina

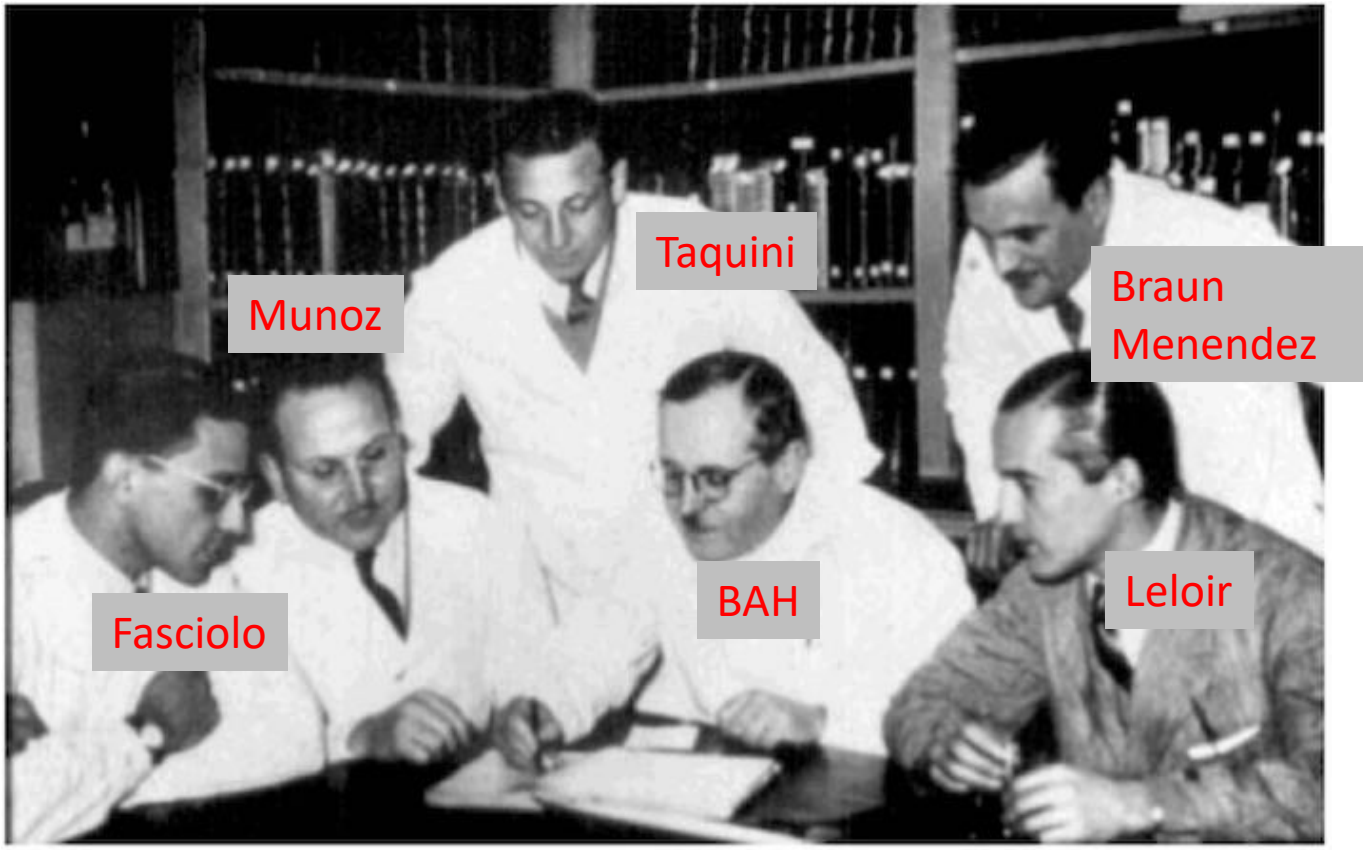



Fig. 1.– Integrantes del grupo de investigadores argentinos cuya labor culminó con el descubrimiento de la angiotensina (año 1940). De izquierda a derecha, sentados: JC Fasciolo, JM Muñoz, BA Houssay y LF Leloir. De pie: AC Taquini y E Braun Menéndez.

*H Valdes-Socin. Histoire des Sciences Médicales 2018 Tome I, p65-72.*

# El joven Houssay

BAH en 1900, à l'âge de 13 ans

Practicantes del *Hospital de Clinicas José de San Martin*
Facultad de Medecina. Buenos Aires

- Nace el 10 de abril 1887 à BsAs
- Bachiller a los 13 años.
- Pharmaceutico a los 17 años.
- Profesor de Fisiología, Faculté de Veterinaria a los 23 años. (1910-1919)
- Médico a los 24 años (1911).

*H Valdes-Socin. Histoire des Sciences Médicales 2018 Tome I, p65-72.*

# Los perros de Houssay

106 104 105

Fig. 47. — A los 124 días de la operación y 200 de edad.

Tesis de HE Houssay
(uno de los hijos médicos de BAH).
*Coleccion privada*

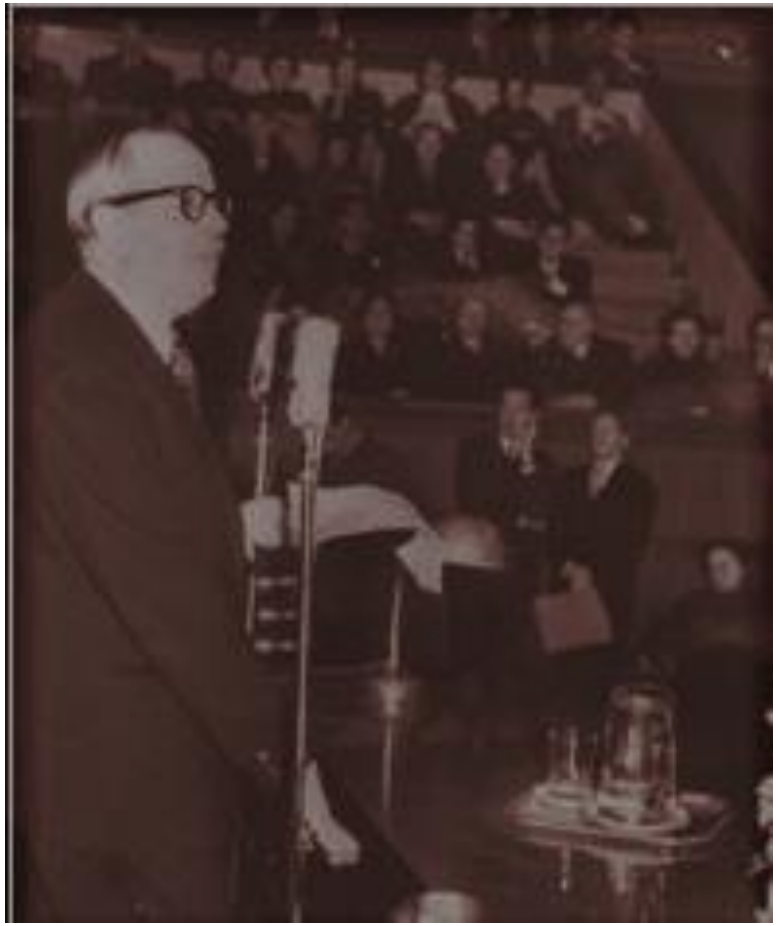
- Las inyecciones de extractos hipofisarios en el perro pancreatectomizado, agravan la diabetes y la hacen permanente (diabetes metahipofisaria)
- Los extractos del lóbulo anterior de la hipófisis tienen una acción hiperglucémica, glucosúrica y cetonúrica en diferentes especies de animales, y por lo tanto un efecto diabetogénico
- La diabetes en animales sin glándula pituitaria o páncreas está mejor controlada

# Buffo Arenarum Henle (BAH)

- Estudios de los efectos de extractos hipofisarios
- Estudios de la blacion del injerto de hipófisis.
- Fisiología comparada de diferentes especies animales

# Premio Nobel de Medecina o de Fisiología 1947
# « Efectos diabetógenos de la hipófisis »


# Creación del Consejo Nacional de la Investigación Científica y Técnica –CONICET- (1958-1971)

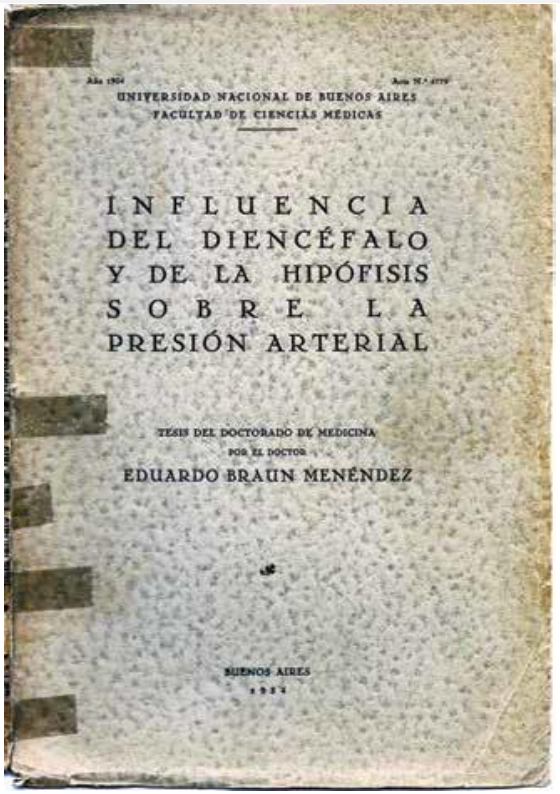


- A partir de 1955 recuperó la cátedra y el apoyo al desarrollo de la investigación a nivel nacional.

- El 5 de febrero de 1958 se convirtió en el primer presidente del Consejo Nacional de Investigaciones Científicas (Conicet). Crea la carrera full time del investigador.

# Prof Eduardo Braun Menéndez (1903-1959 )

[Años 50] En el laboratorio del IBYME



UNIVERSIDAD NACIONAL DE BUENOS AIRES
FACULTAD DE CIENCIAS MÉDICAS

INFLUENCIA DEL DIENCÉFALO Y DE LA HIPÓFISIS SOBRE LA PRESIÓN ARTERIAL

TESIS DEL DOCTORADO DE MEDICINA
POR EL DOCTOR
EDUARDO BRAUN MENÉNDEZ

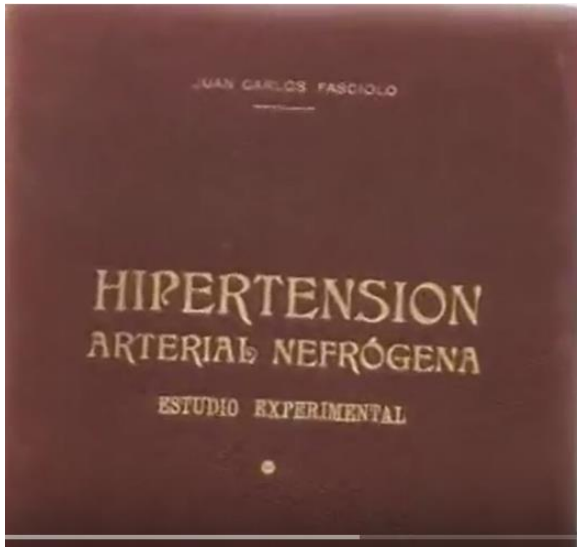
BUENOS AIRES

- Obstáculo venoso en el riñón normal o desnervado e hipertensión arterial. *Rev Soc Argentina de Biología 1932/ Soc Biol Paris 1933*
- Stage en UK con Charles Arthur Lovatt Evans (1884–1968) y vuelve en 1938

*« Estuve a algunos milímetros de hacer un descubrimiento fantástico.*
*Clampeando la arteria renal en lugar de la vena renal, me habría adelantado varios años a Golblatt.*

# Prof Juan Carlos Fasciolo (1913-1993)

- Discipulo de Houssay
- Tesis de Medicina: *Hipertensión arterial nefrógena. Estudio experimental*
- Profesor de Fisiopatología. Univ Nacional de Cuyo




# Prof Alberto Carlos Taquini (1905-1998)

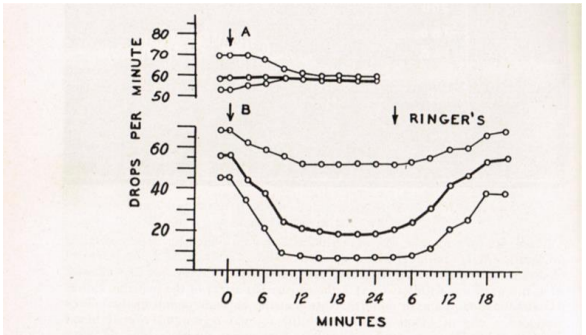


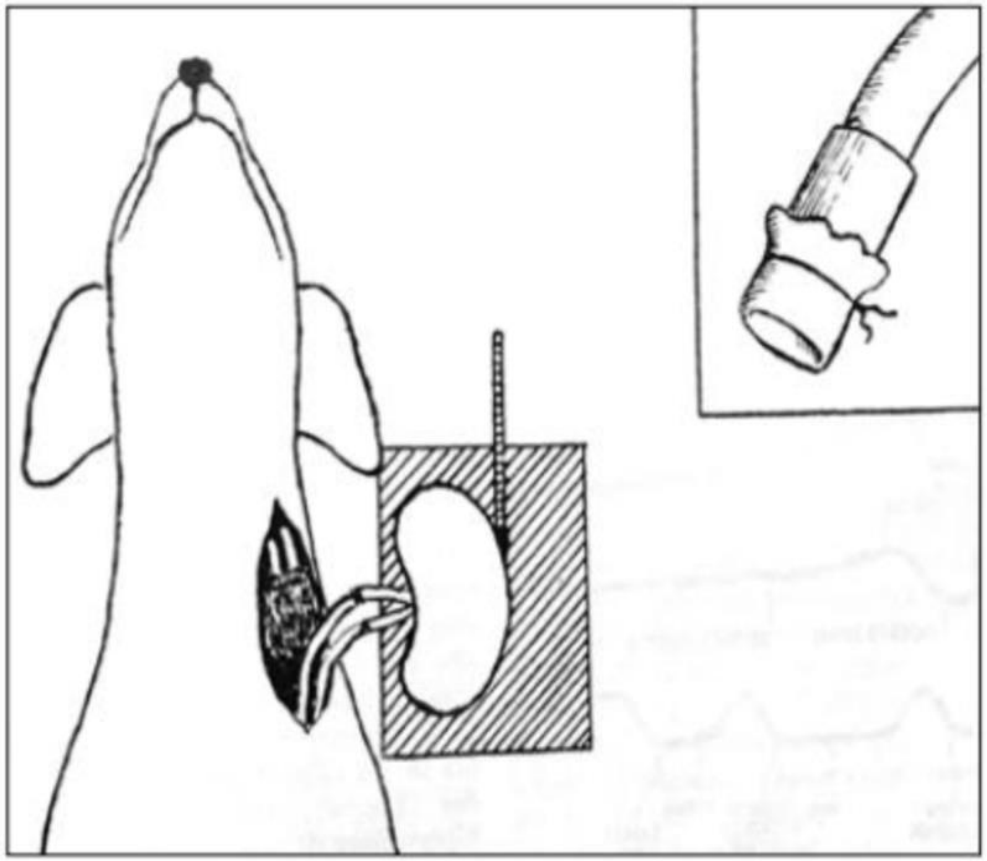

FIGURE 28. VASOCONSTRICTOR ACTION OF RENAL VENOUS BLOOD ON THE VASCULAR SYSTEM OF THE TOAD, *Bufo Arenarum* HENSEL ACCORDING TO THE LÄWEN-TRENDELENBURG METHOD

A: Venous blood plasma from normal kidneys; B: Plasma from venous blood of ischemic kidneys of hypertensive dogs. The fine lines represent the greatest and least vasoconstriction observed with each type of plasma. The heavy lines represent the average action of the plasma from 15 dogs tested on 20 toads. Note the constrictor action of the renal venous blood of hypertensive dogs (After Houssay and Taquini, Rev. Soc. argent. de biol., 1938, *14*, 5).

- En 1938, Alberto Carlos Taquini (1905-1998), observa que el aumento de la presión arterial que se veía luego de restituir el flujo en riñones isquémicos era provocado por la misma sustancia vasopresora involucrada en los estudios anteriores.
- De 1968 a 1971 fue el primer Secretario de Estado de Ciencia y Tecnología de Argentina.
- Director instituto Cardiología, Prof Emérito de Medicina, Miembro Academia de Medicina

Taquini AC, Braun-Menéndez E. Liberación de substancia vasoconstrictora en el riñón completamente isquemiado. Rev Soc Arg Biol 1938; 14: 422-9.

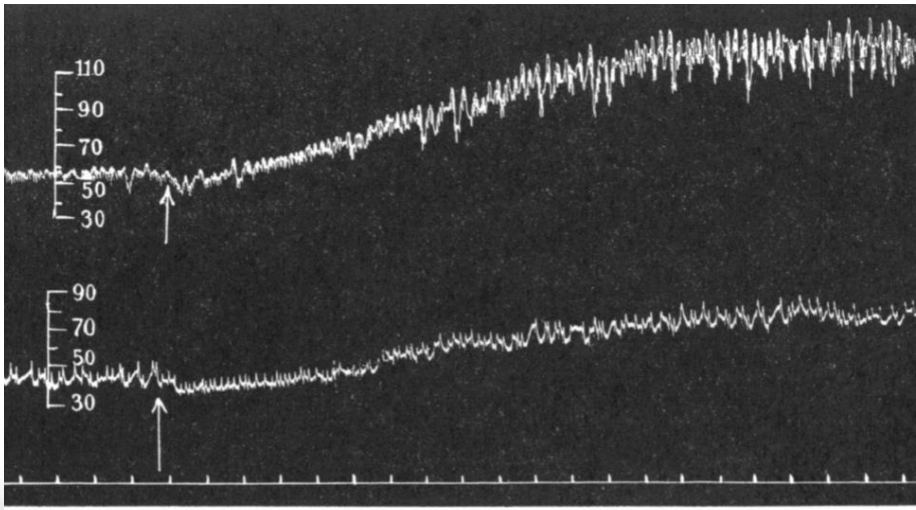
# Implante de rinón isquémico en el cuello del perro



(Figura 1) Esquema de un injerto de riñón en el cuello de un perro. Está representada esquemáticamente la platina calentada con el termómetro. A la derecha, modo de preparar vasos con la cánula de Payr.

- HTA 22/24 perros néphectomisés,
- durée 2-40 jours

**Houssay & Fasciolo 1937**

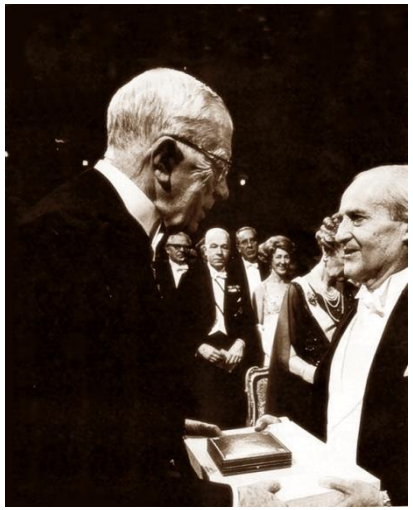



ig. 9. The arrow indicates the grafting of the ischaemic kidney from two hypertensive do
into the neck of two adrenalectomized and nephrectomized dogs.

# Prof Luis Federico Leloir (1906-1987)

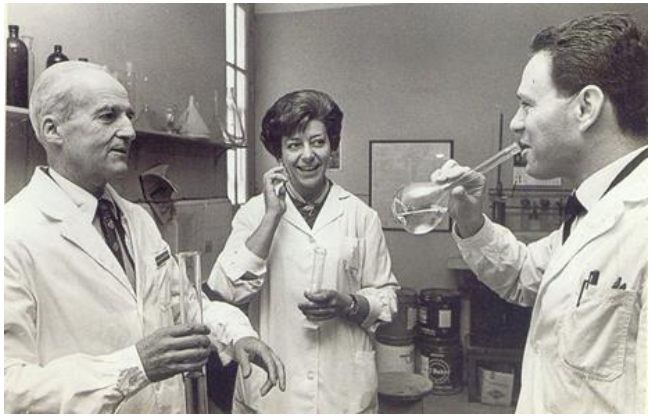

Tesis: "Suprarrenales y Metabolismo de los hidratos de carbono", 1934

# Prof Luis Federico LELOIR (1906-1986)



Prix Nobel de Chimie, 1970

Prof Bernardo A Houssay
Y Luis Federico Leloir (*circa* 1970)



10 Diciembre , 1970,
Luego del Nobel .

-Descubrimiento de la uridina fosfoglucosa (UDP)
-Síntesis de polisacáridos
- La causa de la galactosemia


*Coleccion privada*

J. Physiol. (1940) 98, 283–298 612.146:612.461.269

# THE SUBSTANCE CAUSING RENAL HYPERTENSION

By E. BRAUN-MENENDEZ, J. C. FASCIOLO,
L. F. LELOIR and J. M. MUÑOZ

*Instituto de Fisiología, Facultad de Medicina, Buenos Aires*

(*Received* 13 *February* 1940)

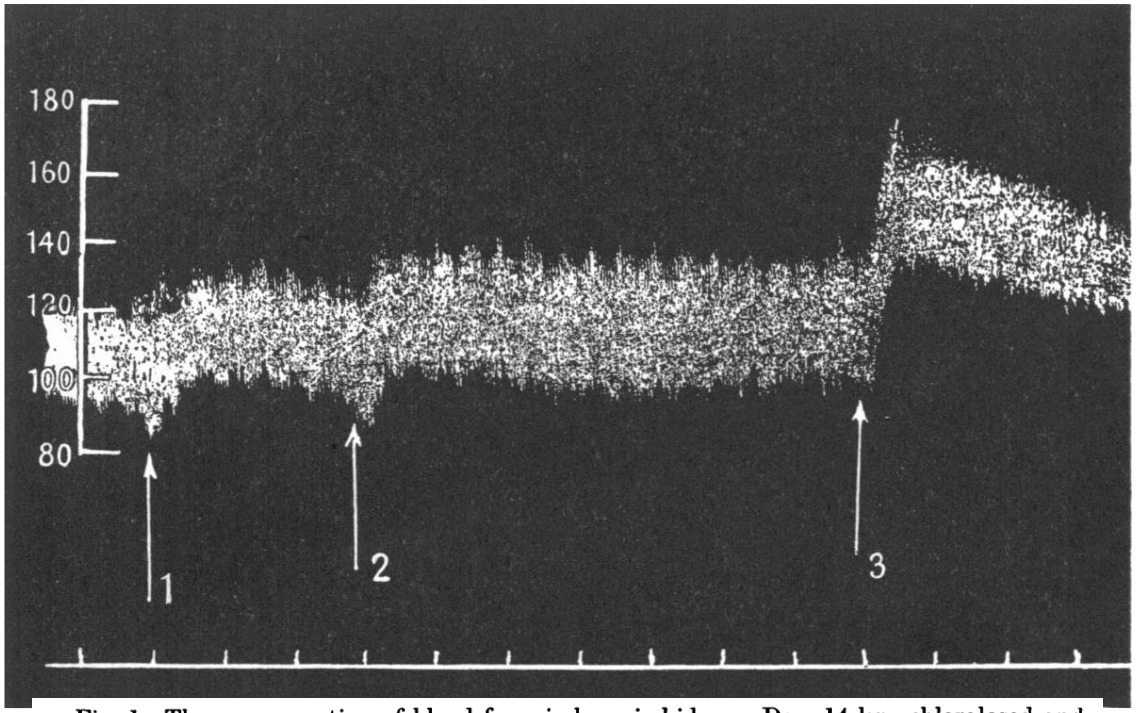



Fig. 1. The pressor action of blood from ischaemic kidney. Dog, 14 kg., chloralosed and nephrectomized. Femoral blood pressure (mm. Hg). Time in minutes. 1, intravenous injection of 15 c.c. serum of circuit's blood; 2, 15 c.c. serum of circuit's blood after 10 min. asphyxia of the heart-lung preparation; 3, 15 c.c. serum of venous blood of perfused ischaemic kidney.

# Identificación de la Hipertensina

nature
International journal of science

Altmetric: 0 Citations: 14 More detail »

Letter

## Hypertensin: The Substance Causing Renal Hypertension

J. M. MUÑOZ, E. BRAUN-MENÉNDEZ, J. C. FASCIOLO & L. F. LELOIR

*Nature* **144**, 980 (09 December 1939)
doi:10.1038/144980a0
Download Citation

Published: 09 December 1939

- Hipertensión por compresión de la arteria renal o inyección de sangre renal venosa
- La substancia llamada **hypertensina** (angiotensina), es diferente de : adrenalina, tiramina, pitresina y urohypertensina.
- La renina es una enzima proteolítica de tipo papaína que libera **hypertensina**, proteína de la fracción pseudoglobulina.

# La Renina es una enzima

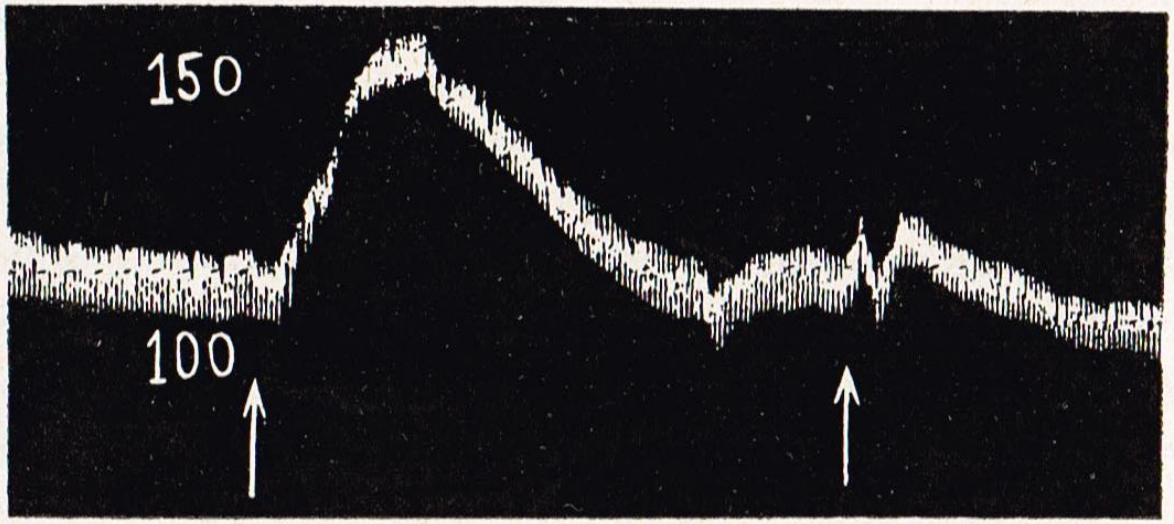
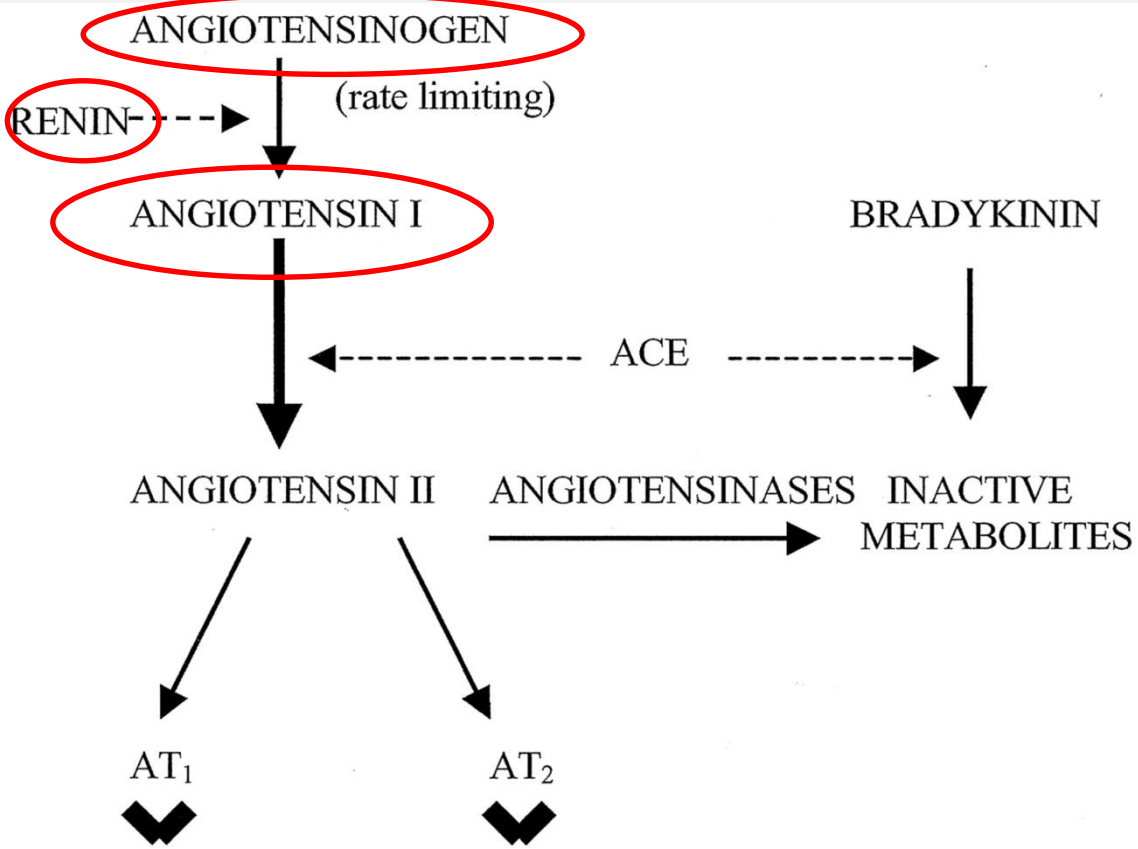



FIGURE 50. DISAPPEARANCE OF HYPERTENSINOGEN FROM PLASMA BY THE INJECTION OF RENIN

Hypertensinogen in the blood of a ten kgm. dog before (first arrow) and after (second arrow) injection of 0.5 cc. of renin per kgm.; ten cc. samples of serum incubated ten minutes with an excess of renin. Rise in blood pressure observed by injection of alcoholic extracts to a chloralosed dog. Blood pressure in mm. Hg (After Muñoz, Braun-Menéndez, Fasciolo and Leloir, Am. J. M. Sc., 1940, *200*, 608)

Reproducen y elucidan las experiencias de 1898 de Tigerstedt y Bergman,
Del instituto Karolinska.




- Vasoconstriction
- Renal sodium reabsorption
- Cell proliferation and dedifferentiation; growth promotion
- Inhibition of renin release
- Stimulation of aldosterone secretion
- Dipsogenic responses

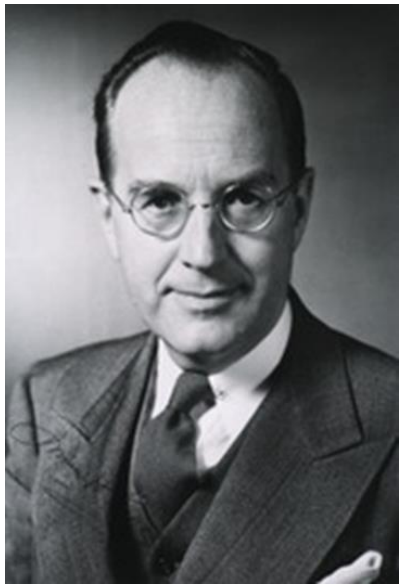
- Functions unknown

From: Carey & Siragi. Newly Recognized Components of the Renin-Angiotensin System: Potential Roles in Cardiovascular and Renal Regulation

Endocr Rev. 2003;24(3):261-271. doi:10.1210/er.2003-0001

# Dr Irving Page (1901-1991)

- Rockefeller Institute
  - Echec d'isolation de la rénine.



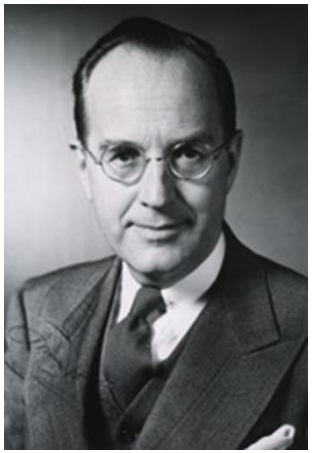
- *Laboratory for Clinical Research .* Indianapolis City Hospital & Eli Lilly company
- Concentran renina a partir de extractos renales: función vasoconstrictora en preparados de cola de perro y oreja de conejo.
- Comprobaron que la vasoconstricción sólo se daba con perfusion suero y no cuando se utilizaba Ringer lactato

- 1945: Director *de the Research Division* à Cleveland Clinic
- 1948: Rapport, Green,and Page isolent, descubren un vasoconstrictor:  la 5-hydroxytryptamina (**serotonina** en el suero

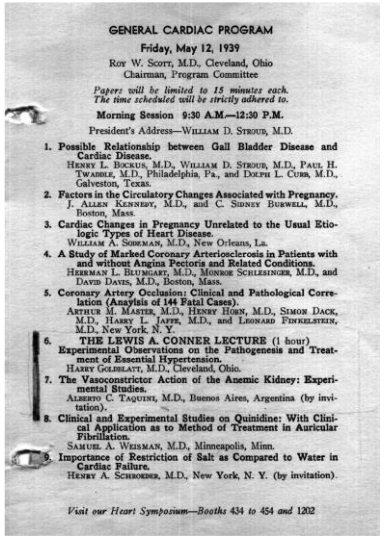
With M. M. Rapport and A. A. Green. Partial purification of the vasoconstrictor in beef serum. J. Biol. Chem. 174:735-41.
With M. M. Rapport and A. A. Green. Crystalline serotonin. Science 108:329-33.

*Irving Page Hypertension Research, A Memoir, 1920-1960*

# 1939, American Heart Association: Duelos cientificos…



- La estrategia del grupo de Page consistió en concentrar la renina de los extractos de la corteza renal y estudiar la vasoconstricción en la cola y la oreja del perro de conejo..
- La vasoconstricción se observó cuando el animal fue infundido con plasma y no con la enfermedad de Ringer Lactato*Kohlstaedt, KG. Helmer, OM. Page, IH. Activation of rennin by blood colloids. Proc Soc Exp Biol Med, 1938, 39:214-215.*
- En 1939, Taquini, que estaba presente en el auditorio, refutó los argumentos presentados por Page: no era un activador de la renina el que causaba vasoconstricción sino otra sustancia diferente.
- 1940: Page et al. Aíslan la angiotonina (hipertensina). Cambiará el nombre de activador de renina a "sustrato" (hipertensinógeno)



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. SOREMAN, M.D., New Orleans, La.
4. **A Study of Marked Coronary Arteriosclerosis in Patients with and without Angina Pectoris and Related Conditions.**
HERMAN L. BLUMGART, M.D., MONROE SCHLESINGER, M.D., and DAVID DAVIS, M.D., Boston, Mass.
5. **Coronary Artery Occlusion: Clinical and Pathological Correlation (Analysis 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).

*Visit our Heart Symposium—Booths 434 to 454 and 1202*

# 1940 Un mismo péptido : dos equipos

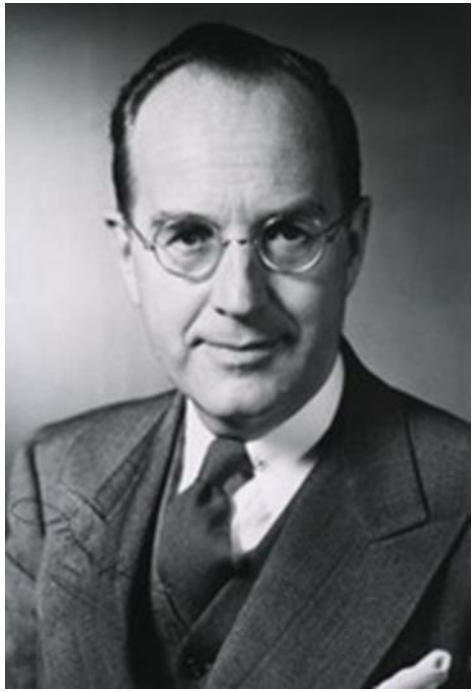
**After this paper had been submitted for publication the report of Page & Helmer, *J. exp. Med.*, 1940, 71, 29, came to our notice. Their results are, in many respects, quite similar to those we have obtained. Further experiments have shown us that ischaemic kidneys secrete renin, hypertensin being subsequently produced in the blood, and also that the destruction of hypertensin by renin is due to impurities of the preparations.**

La renina es una **enzima** (actualmente: aspartyl protéasa)

El hipertensinogeno es sintetizado en el hígado (Leloir et al. Rev Argent Cardiol 1942)

Son una o varias hipertensinasas?

# Una carrera desenfrenada…



- Page y su grupo sintetizan el octapéptido angiotensina.

  Page I, Helmer O. A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin activator. J Exp Med 1940; 71: 29.

- Grupo de Basilea, de **CIBA**, comercializan el octapéptido: Hypertensin™

- Page y su grupo descubren la serotonina à partir de las plaquetas en el suero.

- Rapport, MM; Green, AA; Page, IH (1948). "Serum vasoconstrictor (serotonin). IV. Isolation and characterization". J Biol Chem. 176 (3): 1243–1251

# Síntesis de l'Angiotensina

1958, the Lasker Award

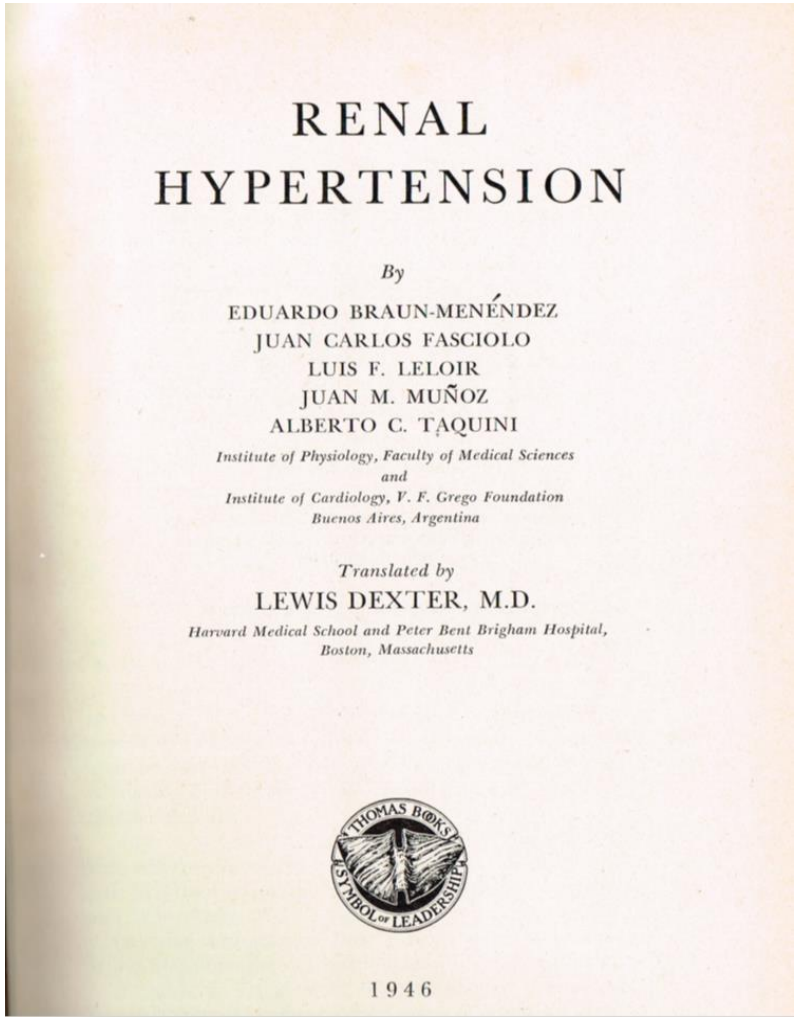
**Sintesis de la angiotensina**

Rittel et al 1957 (CIBA) et Schwartz-Page 1957

Schwarz H, Bumpus FM, Page IH.J Am Chem Soc. 1957

Rittel W et al Helv Chim Acta. 1957

# Argentina: Horas sombrías…



RENAL
HYPERTENSION

*By*

EDUARDO BRAUN-MENÉNDEZ
JUAN CARLOS FASCIOLO
LUIS F. LELOIR
JUAN M. MUÑOZ
ALBERTO C. TAQUINI

*Institute of Physiology, Faculty of Medical Sciences*
*and*
*Institute of Cardiology, V. F. Grego Foundation*
*Buenos Aires, Argentina*

*Translated by*
LEWIS DEXTER, M.D.
*Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts*

THOMAS BOOKS
SYMBOL OF LEADERSHIP

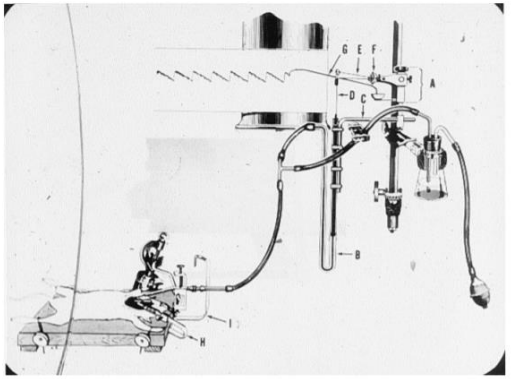
1946

- 1943-1955: Houssay es separado de su cátedra de Fisiología por un gobierno militar.
- Sufre un atentado: una bomba destruye parte de su salón.
- En solidaridad, Menéndez y otros prof renuncian también a sus cargos.
- 1946: Escriben “Hipertensión Renal”

*H Valdes-Socin. Histoire des Sciences Médicales 2018 Tome I, p65-72*

# Descubrimiento de la Angiotensina I y II

- Angiotensina I et II (activa)
- ACE enzima convertidora



Prof Leonard T. Skeggs
(1918-2002)

Décapeptide

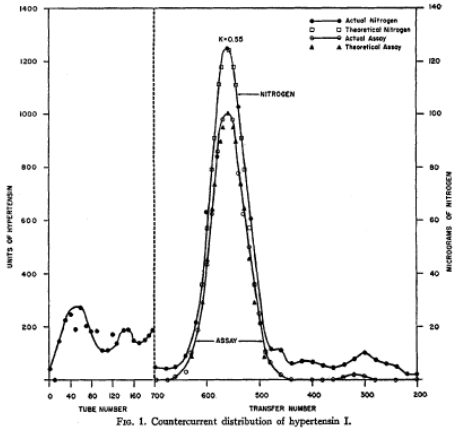



FIG. 1. Countercurrent distribution of hypertensin I.

Octapeptide

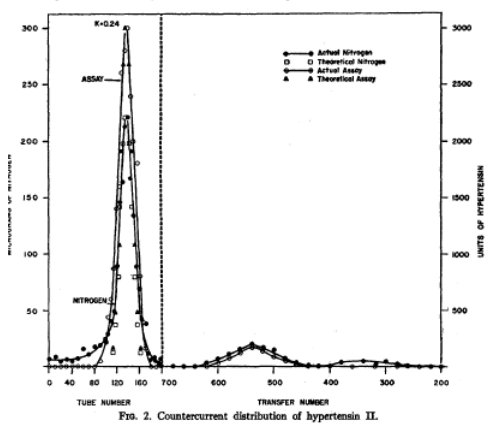



FIG. 2. Countercurrent distribution of hypertensin II.

*Conversion of Hypertensin I to Hypertensin II:*

filtered by vacuum. The filtrate was evaporated under vacuum to a volume of 150 ml., ex-

**Renin Substrate**

**Asp Arg Val Tyr Ile His Pro Phe His Leu Leu Val Tyr Ser R -----**

↓ ← **Renin**

**Angiotensin I**

**Asp Arg Val Tyr Ile His Pro Phe His Leu + Leu Val Tyr Ser R ----**

**Converting Enzyme** → ↓

**Angiotensin II**

**Asp Arg Val Tyr Ile His Pro Phe + His Leu**

*JLeonard Skeggs & al. Exp Med 1954*

# Descubrimiento de la Aldosterona

Sylvia Tait (1917-2003)

James Francis Tait (1926-2014)

Jerome Conn (1907-1994)

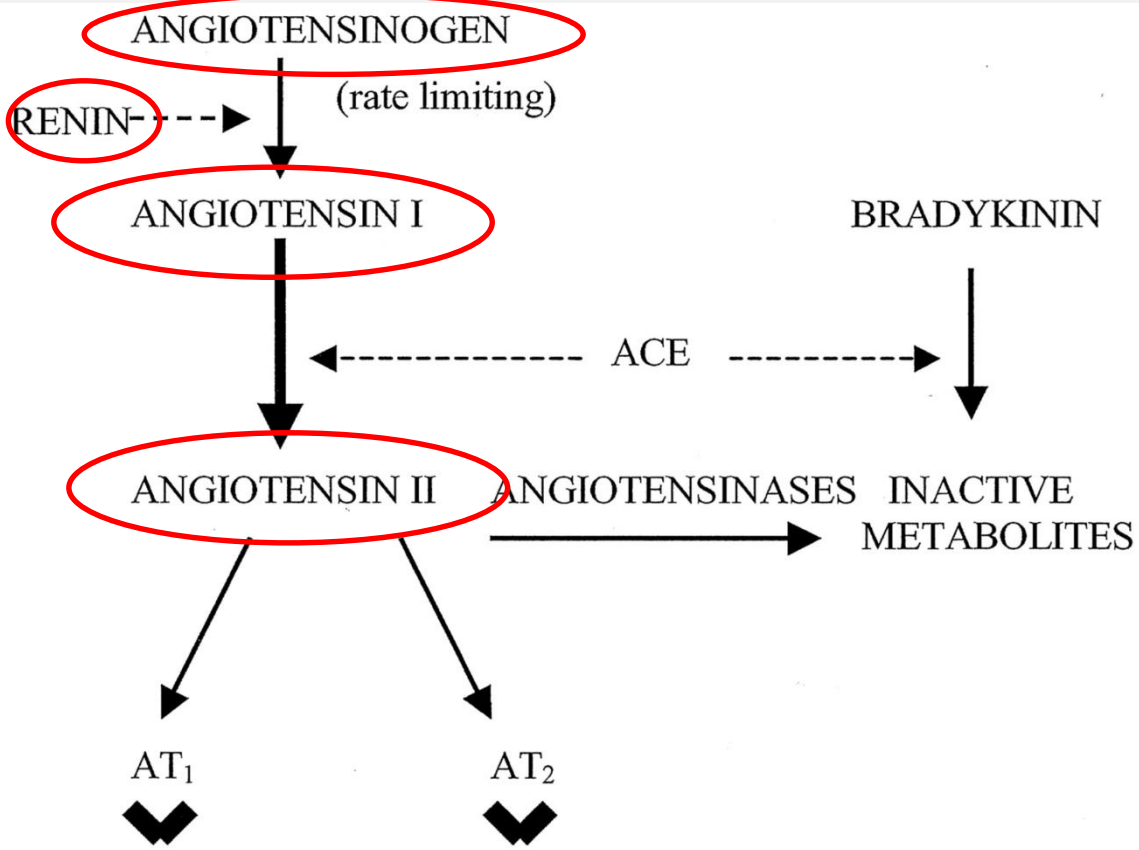
1952: “Isolation of a highly active mineralocorticoid (21mg) from beef adrenal extract (500 mg)”

Electrocortine: ALDOSTERONE

Conn JW 1955 Primary aldosteronism: a new clinical syndrome. J Lab Clin Med 45:3–17.

Conn JW & al. 1972 Primary reninism. (renin-producing juxtaglomerular cell tumors) . Arch Intern Med

H Valdes Socin. The Saga of the Renin-Angiotensine-Aldosterone system. Histoire des Siences Médicales 2021 Tome III




- Vasoconstriction
- Renal sodium reabsorption
- Cell proliferation and dedifferentiation; growth promotion
- Inhibition of renin release
- Stimulation of aldosterone secretion
- Dipsogenic responses

- Functions unknown

From: Carey & Siragi. Newly Recognized Components of the Renin-Angiotensin System: Potential Roles in Cardiovascular and Renal Regulation

Endocr Rev. 2003;24(3):261-271. doi:10.1210/er.2003-0001

# 1943 : Duelo de terminologías

## SUGGESTED CHANGE IN DESIGNATION OF "RENIN-ACTIVATOR" (HYPERTENSINOGEN) TO RENIN-SUBSTRATE ($\alpha_2$ GLOBULIN)

LELOIR, Muñoz, Taquini, Braun-Menendez and Fasciolo[1] have suggested that the term "renin-activator" should be dropped. In discarding it, we believe that the considerations which have influenced our using and retaining the word should be presented as well as those which now prompt us to propose a new term for the same entity.

When Kohlstaedt, Helmer and Page[2] found that renin was not a vasoconstrictor (or pressor) substance except in the presence of another protein present in blood, they identified this other protein as "renin-activator" for the simple reason that in its absence renin was not active. Without any further implication, this observation led to discovery of the pressor substance called "angiotonin" by the North American investigators, Page and Helmer,[3] and "hypertensine" by the workers of South America, Braun-Menendez, Fasciolo, Leloir and Muñoz.[4] In the course of studies on the formation of angiotonin (hypertensine) from the mixture of renin and "renin-activator," evidence was obtained both in this country[5] and in South America[6] which indicated that the interaction was enzymatic and that the so-called "activator" was in fact the substrate. The Argentine group then proposed the use of the terms "hypertensinogen" or "hypertensine precursor" for the substance until that time known as "renin-activator." These terms they developed from the fact that the substance in question gives rise to the pressor substance "hypertensine." However, as has been pointed out editorially in the

[1] L. F. Leloir, J. M. Muñoz, A. C. Taquini, E. Braun-Menendez and F. S. Fasciolo, *Rev. Argent. Cardiol.*, 9: 269, 1942.
[2] K. G. Kohlstaedt, O. M. Helmer and I. H. Page, *Proc. Soc. Exp. Biol. Med.*, 39: 214, 1938.
[3] I. H. Page and O. M. Helmer, *Proc. Cent. Soc. Clin. Res.*, 12: 17, 1939.
[4] E. Braun-Menendez, J. C. Fasciolo, L. F. Leloir and J. M. Muñoz, *Rev. Soc. Argent. Biol.*, 15, 420, 1939.
[5] I. H. Page and O. M. Helmer, *Jour. Exp. Med.*, 71: 29, 1940.
[6] E. Braun-Menendez, L. F. Leloir, J. M. Muñoz and J. C. Fasciolo, *Rev. Asoc. bioquim, Argent.*, 5: 17, 1940.



## DISCUSSION

### ANGIOTONIN OR HYPERTENSIN

IN a letter to SCIENCE, Page, Helmer, Plentl, Kohlstaedt and Corcoran[1] suggest the term "renin substrate" ($\alpha$ 2 globulin) for hypertensinogen or renin-activator. Uniformity of terminology would be desirable, as it has become rather confusing, due to the fact that some substances have several names as follows:

| *Buenos Aires group* | *Indianapolis group* | *Lewis and Goldblatt*[4] |
|---|---|---|
| Hypertensin | Angiotonin | Hypertensin |
| Hypertensinogen | Renin-activator | Hypertensinogen |
| Hipertensinase | Angiotonase[2] | Hypertensinase |
| No equivaent | Angiotonin-activator[3]<br>Angiotonin-inhibitor[3]<br>Renin-inhibitor[3] | No equivalent |

The last three terms have no equivalent in the Buenos Aires group terminology because the existence of the substances or actions implied have not been conclusively proved.

As to which term should be used, angiotonin or hypertensin, it is a matter of personal judgment. No priority can be claimed by either group, as the discovery of this substance was practically simultaneous.

The objection against hypertensin because it "implies a participation in hypertension and an effectiveness in hypotension" would perhaps be valid for commercial use, a point which we have never considered. The term hypertensin appropriately describes its action of increasing blood pressure and, as Lewis and Goldblatt[4] point out, "if it is eventually proved" to be the "cause of the elevated blood pressure, then the specific term hypertensin . . . will be more pertinent than the non-specific term angiotonin." That it has

The term renin-activator should be abandoned because it conveys an erroneous idea. The term hypertensinogen is perfectly correct: in fact, the suffix "ogen" is used to denote "giving rise to" (glycogen gives glucose, fibrinogen, fibrin, caseinogen, casein, etc.). As to the new term proposed "renin substrate ($\alpha$ 2 globulin) it should be pointed out: (1) that the enzymatic nature of the reaction has not "been established beyond a doubt."[1] There are several facts which make it probable, as we have repeatedly pointed out. But the matter can only be settled by experimenting with known concentrations of the pure substances. The fact that reaction approximately follows the equation for a first order reaction[6] can not be taken as a proof. (2) Moreover, if renin is really an enzyme, it might act on more than one substrate. For instance, pepsin acts on many proteins and calling one of them pepsin substrate would not identify it. (3) Adding another term ($\alpha$ 2 globulin) which describes its electrophoretic behavior would not help much. Moreover, it is not yet known whether hypertensinogen is all or part of the $\alpha$ 2 globulin fraction of serum, or only accompanies this fraction, and it remains to be proved that this fraction always contains hypertensinogen.

The addition of a new long and not too happy term for a substance, which has already four, would hardly simplify the terminology.

E. BRAUN MENENDEZ
J. C. FASCIOLO
B. A. HOUSSAY
L. F. LELOIR
J. M. MUÑOZ
A. C. TAQUINI

# 1957: Gentlemen's agreement

- Conferencia de *Ann Arbor* en honor a los 25 años del descubrimiento de Goldblatt.
  - Angiotensinogeno (substrato de la renina)
  - Angiotensinogenasas.

**REPORTS**

Suggested Revision of Nomenclature—Angiotensin

**By EDUARDO BRAUN-MENENDEZ, IRVINE H. PAGE**

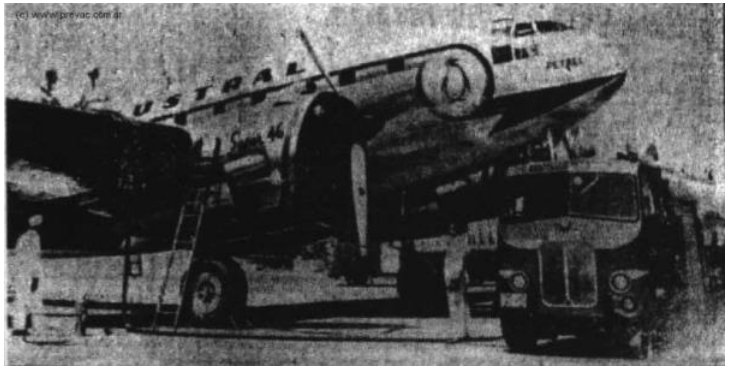
See all authors and affiliations

*Science* 31 Jan **1958**:

Vol. 127, Issue 3292, pp. 242

# 16 enero 1959:
# Tormenta de verano en Mar del Plata

Eduardo Braun Menéndez



Avion Curtiss de la segunda Guerra Mundial

-Crash del vuelo inaugural Buenos Aires-Mar del Plata
-59 pasageros fallecidos incluyendo a Braun Menéndez y su hija
-Un solo superviviente.

# Precursor de la inhibición de la ACE

- 1965 Ferreira & Rocha e Silva
  - Veneno *bothrops jararaca (plantaciones de bananas)*
  - Hipotensión sostenida
  - Péptido que potencializa la bradiquinina
  - Inhibidor de la ACE-1

Dr Sergio Ferreira
(1934-2016)

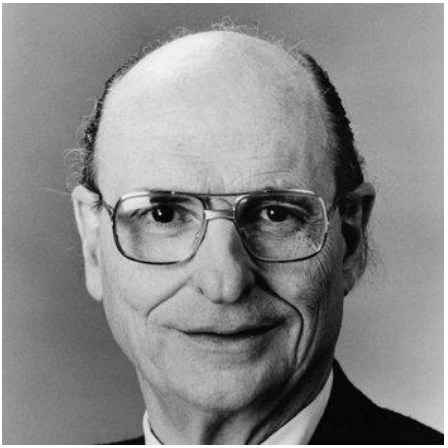
- Ferreira :Royal College Surgeons Londres (trabaja con Sir John Vane, **Nobel 1982**)
  - ACE: inactiva la bradikinina y sintetiza angiotensina (Squibb)

*Bothrops jararaca*

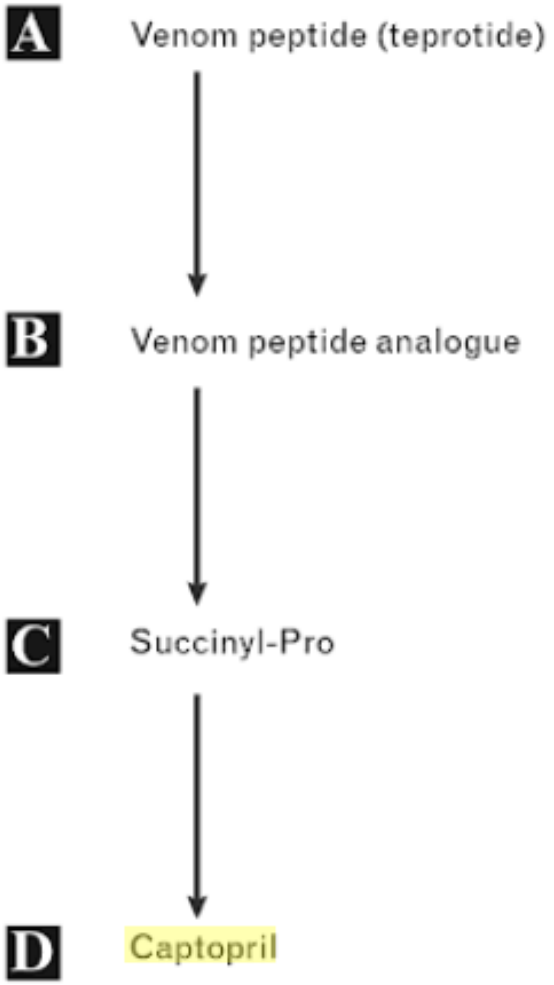
*Ferreira SH. Rocha e Silva M. Potentiation of bradykinin and eledoisin by BPF (bradykinin potentiating factor) from Bothrops jararaca venom.Experientia. 1965;21(6):347–9*

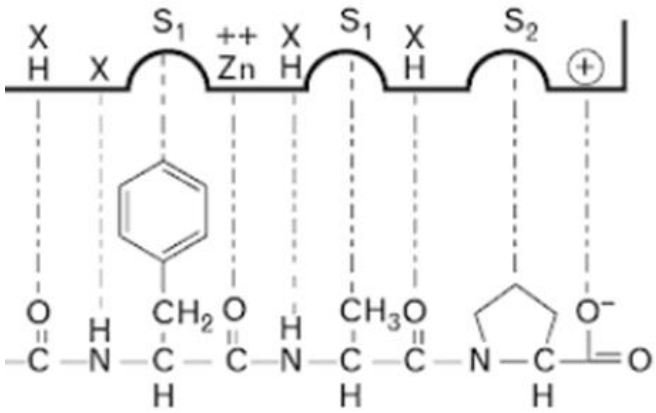
# Miguel Ondetti (1930-2004)

Ondetti M A, Sabo E F. **Angiotensin-converting enzyme inhibitors** from the venom of *Bothrops jararaca*. Isolation, elucidation of structure, and synthesis, Biochemistry 1971; 10 (22): 4033-4039.

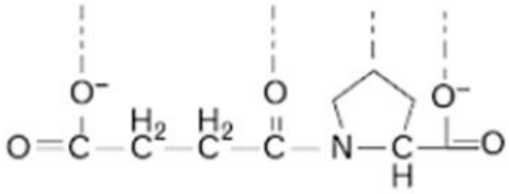


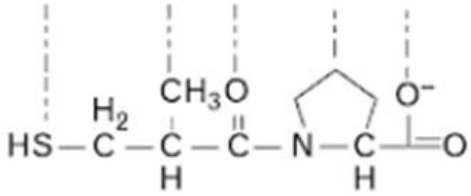
Lasker Clinical Medical Award 1999



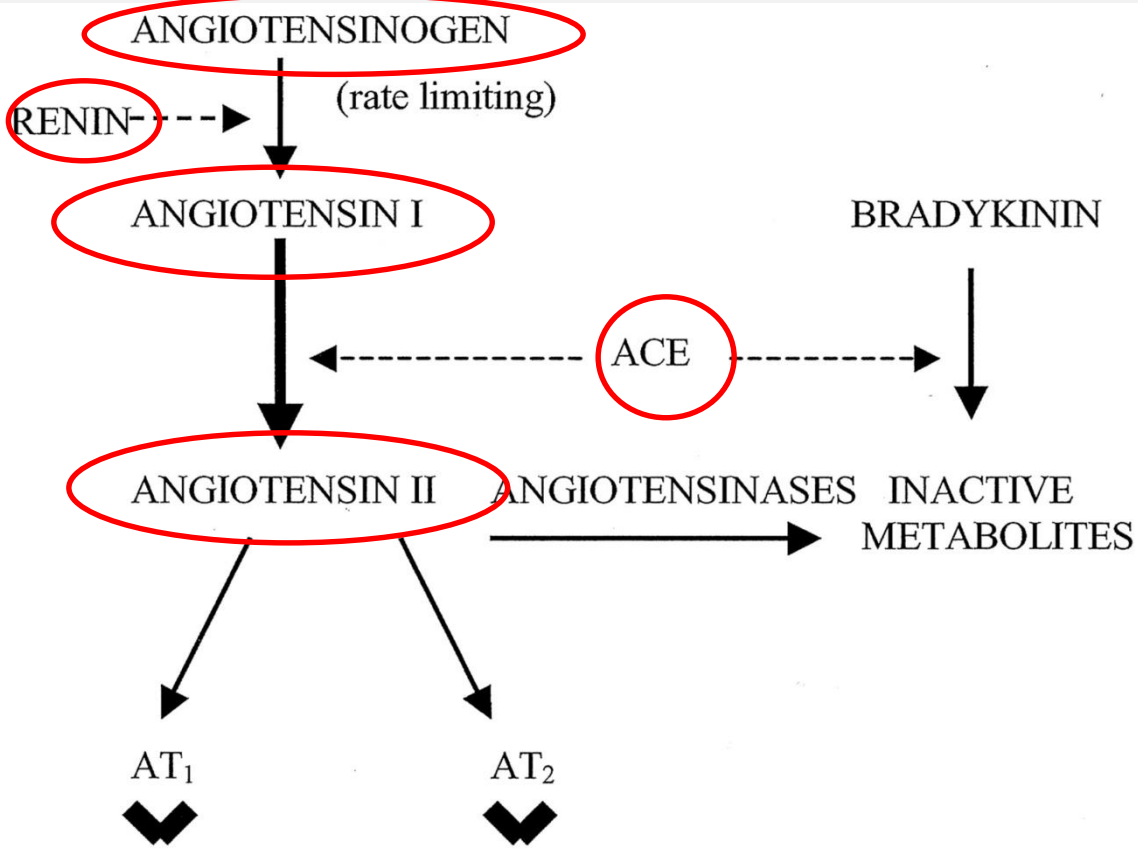



*Ondetti M A, Rubin B, Cushman D W. Science 1977*





**El Captopril** ®(Squibb) es aprobado por la FDA en 1982 para tratamiento de la HTA




- Vasoconstriction
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From: Carey & Siragi. Newly Recognized Components of the Renin-Angiotensin System: Potential Roles in Cardiovascular and Renal Regulation

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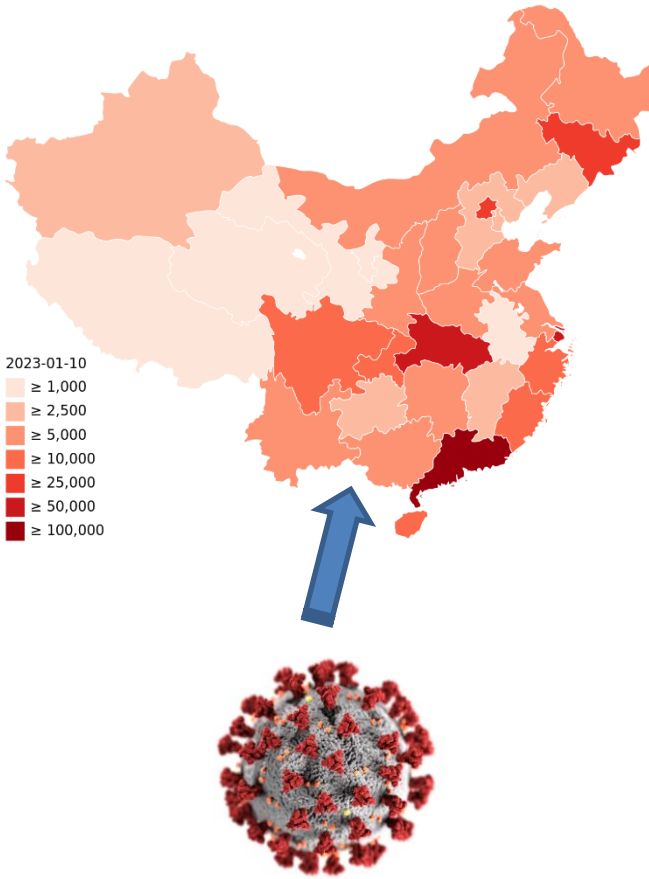
# COVID-19

- En diciembre 2019, una neumonía producida por un nuevo coronavirus ( SARS CoV-2) se registra en Wuhan , provincia de Hub, en China.

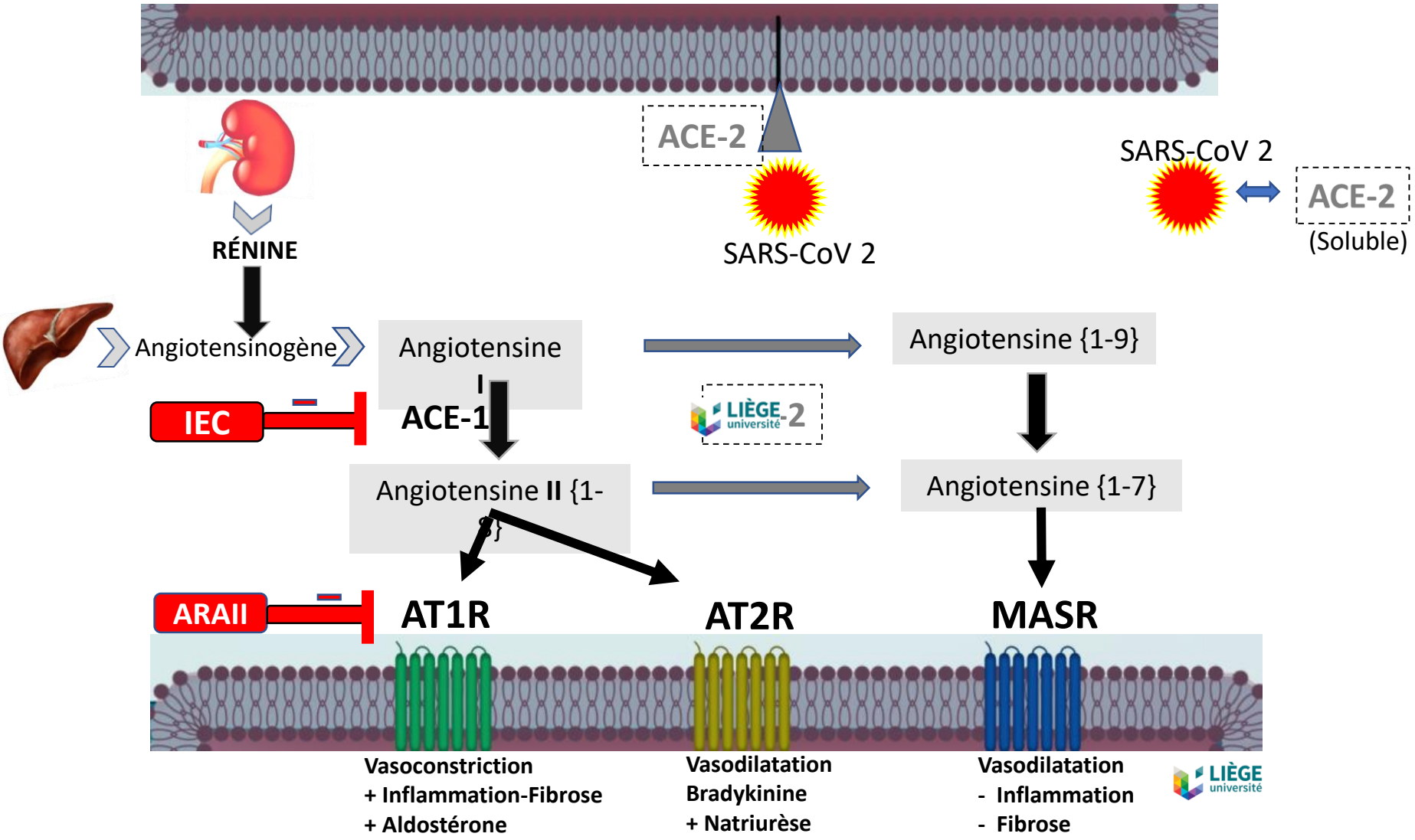
- El virus se fija à la enzima de conversión 2 (ACE-2) , carboxypeptidasa homologa de ACE, en todos los tejidos.
- El coronavirus disminuye la actividad de d'ACE-2. Esta disminución seria un factor agravante del síndrome inflamatorio pulmonar producido por la COVID-19,

- El 11 de marzo 2020, la pandemia viral COVID-19 invade Europa, América , y se torna planetaria .



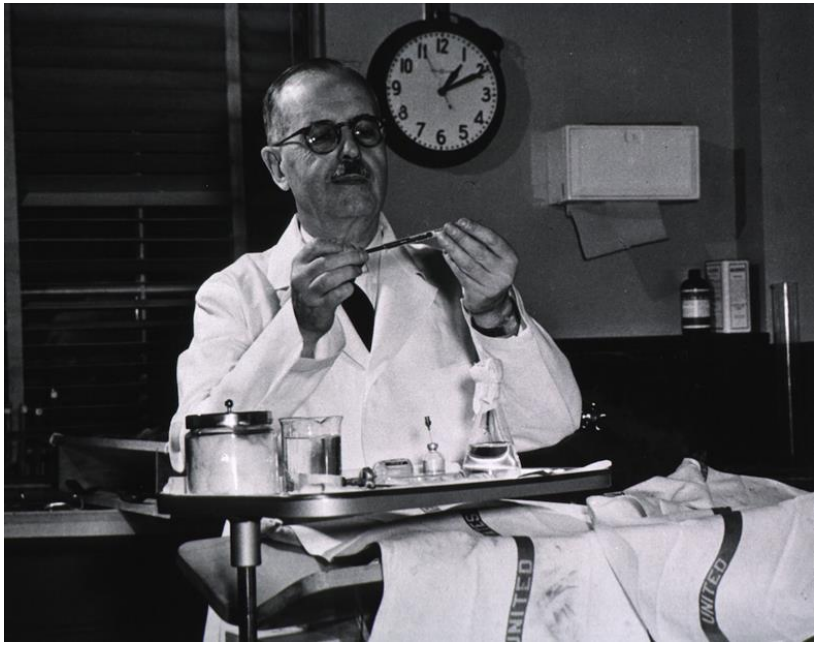

Valdes Socin et al [Renin-angiotensin-aldosterone system : brief history and questions related to the COVID-19 pandemic] Rev Med Liege. 2020;75(S1):123-129

# SRAA y COVID-19




*De: Valdes-Socin H et al. RmLg 2020*
*Valdes-Socin H et al. VCP 2020*

# Conclusiones : Legados de la Fisiología Argentina




*Ricardo Celma*
*(2017)*

*« Tened ideales elevados y pensad en alcanzar grandes cosas, porque si la vida rebaja siempre y no se logra sino una parte de lo que se ansía, soñando muy alto alcanzaréis mucho más. No olvidéis que todas las grandes conquistas del presente son sólo sueños juveniles realizados.*

Discurso de despedida pronunciado el 8 de abril de 1958 UBA