

Meta-analyses inevitably are skewed towards positive findings as negative results rarely get published [as recognized by the 80 000 plus signatories to the All Trials Campaign (www.alltrials.net) run by Bad Science, London, UK, and the Dartmouth Institute of Health Policy and Clinical Practice and the Geisel School of Medicine, Hanover, New Hampshire, USA]. Also, not all published studies are of equal weight, and a run of small studies, say, might be insignificant compared with one well-run, large study. Equally, meta-analysis itself may be biased by an overt or subliminal agenda, coupled with lack of information on conflicts of interest in the studies being analysed. Even so, Archie Cochrane and well-conducted meta-analyses have lifted medicine out of the dark ages!

Five years after Cochrane's death, his name was given to a centre for analysis of published trial data, set up in Oxford, UK, by the NHS Research and Development Programme. It was keen to build on the success of the Oxford Database of Perinatal Trials compiled by the National Perinatal Epidemiology Unit, directed by Dr Iain

Chalmers (later knighted), who was given the job of setting up the Cochrane Centre. From these small beginnings, the ideas of Archie Cochrane have blossomed into The Cochrane Collaboration, an international network which involves >31 000 participants in >120 countries.

Just as the Encyclopédistes >200 years ago attempted to sift known information into authoritative articles, Cochrane was formed to organize medical information systematically to help all parties in healthcare make interventions on the basis of evidence. The outcome is *Cochrane Database of Systematic Reviews*, available online, together with some reviews published in parallel in the medical literature. In 2011, WHO granted Cochrane a seat on the World Health Assembly.

To date, Cochrane has 53 specialty-based groups, including ones on heart, hypertension, stroke, and peripheral vascular disease. Its author base is international, although about one-third are from the UK, where half of its groups are also based.

75th anniversary of the discovery of angiotensin: a tale of two countries

This paper was written in collaboration between the University of Perugia, Italy and the Instituto de Investigaciones Cardiológicas, Universidad de Buenos Aires-Conicet, Argentina



Figure 1 Original portrait of Harry Goldblatt autographed 'To Dr Taquini with kindish regards'.

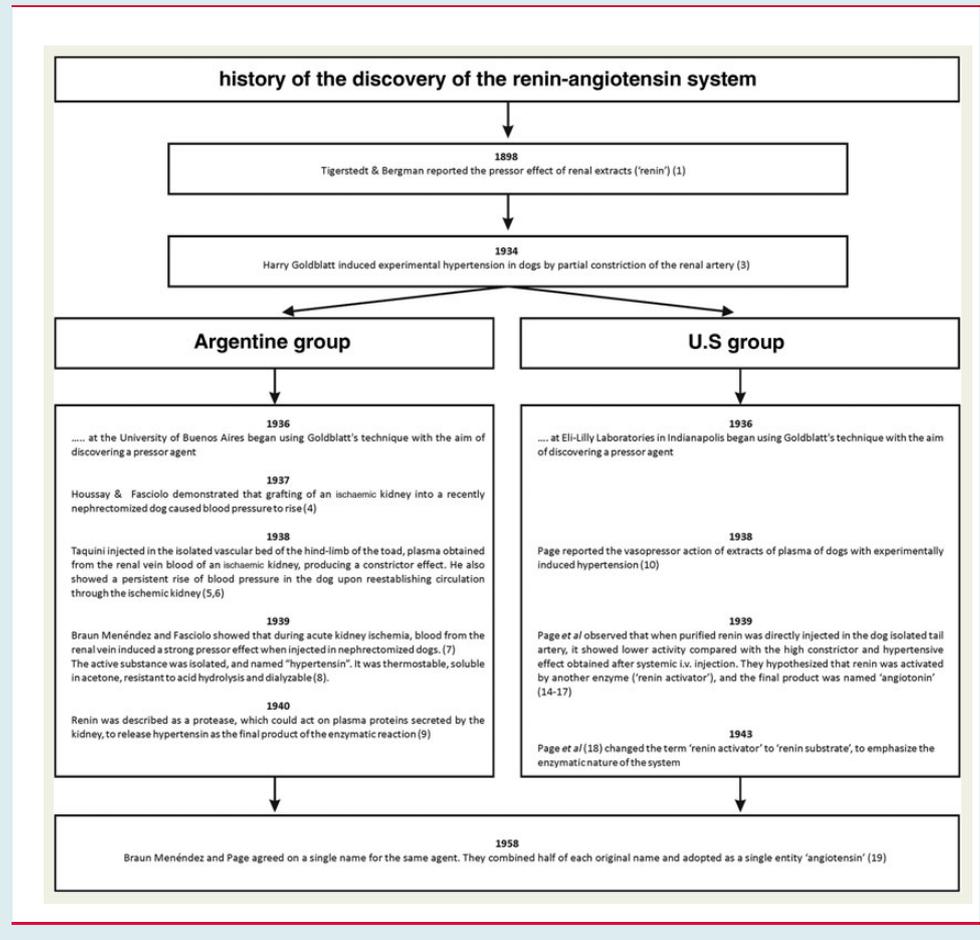
The 75th anniversary of the discovery of angiotensin was recently celebrated in Buenos Aires at the 70th anniversary of the founding of the Instituto de Investigaciones Cardiológicas 'Prof. Alberto C. Taquini'. Tracing the story of angiotensin's discovery highlights the impressive degree of excellence gained by Argentine biomedical research during the middle of the twentieth century. Most importantly, it unfolds a remarkable piece of medical research and of trans-national competition and eventual cooperation.



Figure 2 The Argentine group, 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).

As early as 1898, Tigerstedt and Bergman had reported a pressor effect of renal extracts and they called the renal substance 'renin'. However, it was not until almost 40 years later, in 1934, that Harry Goldblatt in a seminal paper demonstrated that clamping of a renal artery in dogs produces hypertension (*Figures 1 and 2; Table 1*).

That observation spurred intensive research at about the same time (1936), on both sides of the American continent, which in just

Table 1 Discovery of the renin-angiotensin system

a few years shed much light on the mechanisms of the vasopressor response originally described by Goldblatt.

In 1937 in Buenos Aires, Bernardo Houssay (who received the Nobel Prize in 1947), foreseeing the presence of a humoral mechanism, asked Juan Carlos Fasciolo a young medical graduate, to reproduce Goldblatt's technique. Very soon, they demonstrated that ischaemic kidneys release a substance that increased blood pressure when injected into nephrectomized dogs. Just after that, in 1938 using a similar approach, Alberto C. Taquini also in Buenos Aires, proved that the rise in blood pressure which follows re-establishment of circulation in ischaemic kidneys was also produced by the release of the same vasoactive compound.

By the end of 1938, Federico Leloir, 1970 Nobel Prize winner and Juan M. Muñoz, joined the group as chemists in order to collaborate to identify and characterize the vasoactive substance. At this point, Houssay had been able to gather a formidable team of scientists to investigate the subject, formed by Eduardo Braun Menéndez, Fasciolo, Leloir, Muñoz, and Taquini (Figure 2).

In a short time, they isolated a pressor agent from the plasma of venous blood of acute ischaemic kidneys. The substance could be extracted with 70% acetone, was dialyzable, thermostable, and with a short pressor effect; they called it 'hypertensin'. Shortly thereafter

they also proved that it was the result of an enzymatic reaction in which renin was the enzyme and plasma the substrate.

At the same time, similar research was very actively being pursued in North America.



In 1937, Irvine H. Page and colleagues in Indianapolis postulated that renin has to be activated by plasma to become vasoactive, and produce hypertensive effects.

They presented their work at the American Heart Association Annual Meeting on 12 May 1939 in St Louis, Missouri (Figure 3). This was the meeting point which allowed the two groups to exchange their experiences. In fact, Taquini was present at the meeting, as he had been invited to present his work with totally ischaemic kidneys (Figure 4).

Four decades later, he related 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 co-workers interpretation. Apparently, Goldblatt who was also present was the only one to take my comments into consideration. At the end of the sessions he invited me to stop at his

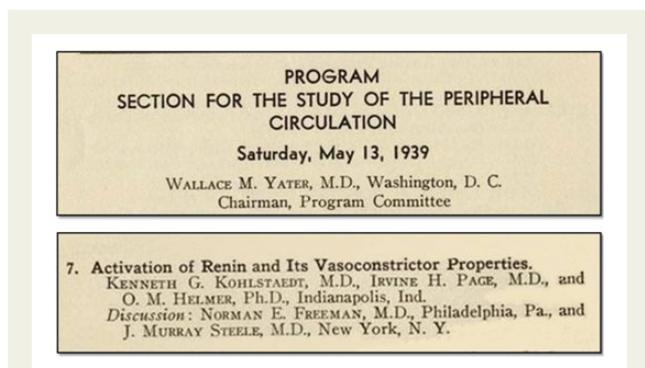


Figure 3 Fragment of the original program from the scientific sessions of the American Heart Association of 1939 with Page's presentation.

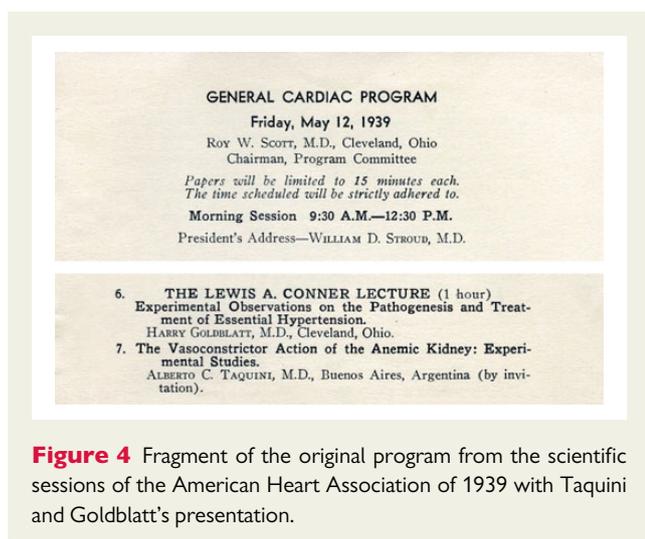


Figure 4 Fragment of the original program from the scientific sessions of the American Heart Association of 1939 with Taquini and Goldblatt's presentation.

laboratory on my way back to Boston in order to analyze the problem more extensively . . .

In the years that followed the discovery of angiotensin, the Argentine group studied its enzymatic release from angiotensinogen, the secretion of renin by kidneys, identified angiotensin as a peptide, and studied the formation of angiotensinogen by the liver. The final contribution of the group was the book 'Renal Hypertension'.

On the other side, Page and co-workers observed that when renin was directly injected in the isolated dog tail artery, it showed lower activity compared with the high-hypertensive effect obtained after systemic injection. They hypothesized that renin was activated by another enzyme, and the final product was named 'angiotonin'.

Page *et al.* acknowledged in 1943 the enzymatic nature of the system and renamed their so-called 'renin-activator' as 'renin substrate' (angiotonin).

At the end of 1943, the Buenos Aires team disbanded. Braun Menéndez continued his work together with Houssay in the

private Instituto de Biología y Medicina Experimental. He became a full professor of Physiology at the University of Buenos Aires in 1956. Unfortunately, he died in an aeroplane crash at the peak of his career in 1959.

Leloir (1906–87) moved on to work as a fellow in Carl F. Cori's laboratory in St Louis in 1944 and subsequently returned to Buenos Aires and worked on the metabolism of galactose, which led him to the Nobel Prize in Chemistry in 1970 for his discovery of sugar nucleotides and their role in the biosynthesis of carbohydrates.

Fasciolo (1911–93) worked with Taquini until he became full professor of Physiology at Cuyo University in Mendoza. He continued his research on hypertension until his death. He was the mentor of multiple investigators, among them, Alberto Nasjletti, Oscar Carretero, and Juan C. Romero, who crowned brilliant careers in internationally renowned centres.

Taquini founded the Instituto de Investigaciones Cardiológicas in 1944, which he directed for 54 years until his death in 1998. During his long and fruitful life, he received more than a hundred national and international awards, published >350 papers in high-impact factor journals and formed a legion of disciples. Of note, autobiographical notes and some unpublished documents related to the discovery of angiotensin and to this very report, remained hidden for >60 years in a drawer of his desk, only to be found by one of us (J.M.) at the time of his taking charge as director of the institute.

After another decade of intensive and at times competitive work among the two Institutions, both teams eventually became concerned about the confusion and the controversies generated in the field by the duplication of terms 'hypertensin-angiotonin'; accordingly, they agreed to use a single name to denote the same pressor agent, and cleverly decide to fuse the two original names into 'angiotensin', at a meeting in Michigan in 1958.

Over time, the 'adventure of the discovery of angiotensin', using unsophisticated methods compared to present day technology was no longer an adventure and it became a reality.

