The Discovery of Angiotensin

... 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 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.

Added to this finding was an incident bringing forcibly to my attention that we were not simply concentrating a pressor agent. A sample of renin was left on my desk for several days without being tested. When I finally came to it, the sharp rise in arterial pressure to well over 300 mm Hg was startling. The curve of blood pressure rise was instantaneous and not at all like that of renin. These two observations formed the basis for the discovery that a new substance had been formed, and the characteristics of the reaction strongly suggested an enzymatic reaction. Perfusing the dog's tail or rabbit's ear with plasma and injecting renin into it showed a clear increase in vasoconstriction as purification proceeded. The active agent was called "angiotonin."


Concurrent with our work was that of Braun-Menéndez, Fasciolo, Leloir, Muñoz, and Taquini, demonstrating the occurrence of a vasoconstrictor substance in the venous blood of ischemic kidneys. They also concluded that what they called "hypertensin" was the result of an enzymatic reaction.

As I already mentioned, angiotonin and hypertensin became angiotensin as a result of a meeting between Eduardo Braun-Menéndez and myself over two martini cocktails. The proceedings of this delightful meeting became a joint note in Science (1958). The story has been told in more detail by Fasciolo (1974) and by me (1975).

More interesting is the history of renin and angiotensin since 1939. First, the announcement of the discovery of angiotensin created almost no interest. Many doubted angiotensin's existence, among them oddly enough being Harry Goldblatt. Even when relatively clean preparations were made available, work on it was desultory.

In early 1938 we had reported on what we then called, "the activation of renin by blood colloids." 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 (Page, 1939), in which the pressor activity of renin was shown to be dependent on the presence of renin—"activator" or substrate.

On May 13, 1939, the presence of this new substance was reported at the annual meeting of the AHA. Through a misunderstanding with the editor of the American Heart Journal, Fred Smith, the papers were not published, even though the manuscripts from the meeting had been required by the AHA. It was not until November that the difficulties were erased and the report of the May meeting published. However, the completed manuscript did not appear until January 1940, but now in the Journal of Experimental Medicine thanks to Peyton Rous. Consequently, we submitted a paper to the Central Society for Clinical Investigation in September 1939, which was presented in November (Page and Helmer, 1939).

Studies of Braun-Menéndez and Colleagues
Houssay and Fasciolo (1937) grafted ischemic kidneys of dogs with chronic renal hypertension onto the vessels of normal and nephrectomized dogs. An immediate large increase in arterial pressure occurred, while little change was produced by grafted normal kidneys. Houssay and Taquini (1938) collected venous blood from normal and ischemic kid-
neys, diluted it with citrate and Ringer's solution, and assayed it on a Läwen-Trendelenberg frog preparation. Vasoconstriction occurred only in blood from the ischemic kidney. Grimson (1939) confirmed this finding. Braun-Menéndez et al. (1939) and Muñoz et al. (1939) found that renin acts on blood protein to produce a substance with the same properties as those of the substance in blood from ischemic kidneys.

The details of these experiments appeared first in July 1940 in a report by Braun-Menéndez et al. (1940). A number of its pharmacologic properties were studied, but no substantial chemical characterization of it was made.

It thus seemed clear to us all the time relations were so close that it would be senseless for either of us to claim priority. We agreed to share any praise or blame (Braun-Menéndez and Page, 1958). The detente made it easily possible to fuse the two original names, angiotonin and hypertensin, into "angiotensin" and hopefully to abolish the misleading terms, renin-activator and angiotensinogen, substituting "renin-substrate." To say the least, this agreement provided one less committee with nothing left to do!

Our group interested in the chemistry of angiotensin by this time in Cleveland, led by Merlin Bumpus, was busy, like others, trying to find the amino acid sequence of what proved to be an octapeptide. The first correct sequence was achieved by Elliott and Peart at St. Mary's Hospital in London and by Skeggs at the Veterans' Administration Hospital in Cleveland. This was followed by the synthesis of angiotensin by Bumpus, Schwarz, and Page and concurrently by Robert Schwyzer and his large group at Ciba in 1957. The availability of the synthetic peptide startlingly increased interest in the substance.

Peart had isolated from the incubation mixture of renin and substrate a pressor peptide with 10 amino acids, whereas Skeggs et al. obtained a mixture of two vasoactive peptides which they termed hypertensin I and II. Hypertensin I was converted to hypertensin II by a chloride-activated converting enzyme. Skeggs' converting enzyme, along with angiotensin, was to prove the basis for an important treatment of hypertension, the converting enzyme inhibitor captopril and more recently, enalapril. Indeed the New York Times reported that during 1987, it is estimated that 565 million dollars' worth was sold. It is odd that these enormously successful antiangiotensins had to be discovered in the Squibb and Merck laboratories.

Selected Bibliography
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