A brief history of renin

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Renin was discovered by the Finnish physiologist, Robert Tigerstedt, working with his medical student, Bergman, in Stockholm in 1898. They showed that saline extracts of fresh rabbit kidney or of an alcohol-dried powder produced an initial fall but then a prolonged rise in blood pressure when injected into rabbits lightly anesthetized with urethane [1, 2]. They also showed that renin could only be extracted from the renal cortex, that it was destroyed at 56°C, precipitated by half-saturated ammonium sulfate, did not dialyze, had little effect on the heart, but also raised blood pressure of the pithed cat. For about three decades, very little else happened. When Myron Prinzmetal went to work with George Pickering, the two could initially not duplicate these findings. It was only when they used saline extracts of alcohol-dried kidney in unanesthetized rabbits that they achieved success. Franz Volhard and his assistants also stumbled on the problem of documenting the existence of renin. However, Volhard's student, Hessel, eventually reported success in 1938. Greatly facilitating the notion that renin must exist were the renal artery stenosis studies of Harry Goldblat and collaborators in 1934. In 1938, Fasciolo, Houssay, and Taquini showed that renal venous blood from an ischemic kidney produced vasoconstriction. Shortly thereafter, Braun-Menendez, Fasciolo, Leloir, and Munoz showed that the pressor substance was soluble in acetone, thermostable, and dialyzable, in short nothing at all like renin. They named the substance *hypertensin*. Independently, and in the same year, Irvine Page and Oscar Helmer, working in Indianapolis, IN, USA, found that renin was inactive when perfused in saline through the rabbit's ear but that activity was restored by blood. They also showed that incubating renin with plasma produced a new substance that they called *angiotonin*. Both groups demonstrated that renin acts like an enzyme and a plasma protein as a substrate. In 1954, Skeggs, Marsh, Kahn, and Shumway, working at the Veterans Hospital in Cleveland, OH, USA, isolated two products from incubating hog renin with horse serum, hypertensin I and II. The group then showed that hypertensin II consists of the following eight amino-acids: Aspartic-Arginine-Valine-Tyrosine-Isoleucine-Histidine-Proline-Phenylalanine.
Hypertensin I is a decapeptide, with two additional amino acids, histidine and leucine, added to the phenylalanine end of the chain. Peart, while working in Pickering's laboratory, largely confirmed these findings. The North and South Americans agreed to consolidate the nomenclature so that the deca- and octapeptides are termed *angiotensin* (Ang) I and Ang II, respectively. Thus, by 1956, the renin–angiotensin system was pretty well worked out. As a nephrologist, I would like to make a few more comments about Leonard Skeggs, who in my view is a largely unsung hero. Aside from the structure of Ang I and Ang II, Skeggs developed the plate hemodialyser that bears his name in 1948. This same technology was then adapted by Skeggs to develop the first automated device to perform blood chemistries. It was called the SMA-12-60 autoanalyzer. Incidentally, the late Norman Shumway, who also appears on these papers, is much better known for his seminal contributions to cardiac transplantation.

In 1958, Franz Gross published a brief history of renin, largely as I have recapitulated here [3]. In that paper, Gross made the startling suggestion that somehow renin stimulated aldostserone. He based this conclusion on data from his own laboratory. His group had found that treating animals with aldosterone and salt led to hypertension and a *decrease* in renal renin content. Adrenalectomy led to an increase in renal renin content. Aldosterone deficiency led to sodium loss, which in turn led to increased renin production. In bold strokes, Gross painted the picture of the major mechanisms controlling renin and aldosterone secretion. When Schwyzer succeeded in synthesizing Ang II in sufficient quantities for experimentation, Gross provided others with the material, just in case they might want to see what effect it had on aldosterone secretion. The schema proposed by Franz Gross is shown in Fig.1 and largely represents the renin–angiotensin– aldosterone system as explained to me by Oscar Helmer in Indianapolis, IN, USA, 1968.

Is renin solely a renal phenomenon? No, Ganten et al. showed that renin is also produced in the gut and in the brain [4,5]. Reports of renin-like activity in the female reproductive tract and in anephric dialysis patients were published at about the same time [6,7]. Numerous investigators worked on the existence of a relatively inactive material with a higher molecular weight than renin, termed "big renin." Inagami and Murakami were able to isolate big renin and big-big renin in 1977 [8]. The

relatively inactive big forms could be activated by acid, cold storage, and catalytic reactions. Sealey and Laragh examined this question extensively and further developed the notion of "pro"renin [9]. Luetscher and colleagues assayed renin and prorenin in patients with diabetes and made the seminal, largely ignored at the time, observation that prorenin correlated much better with diabetic complications than did renin levels [10]. Patients with high prorenin concentrations developed renal failure, blindness, and neuropathy. Diabetics generally have low plasma renin activity but relatively high prorenin levels.

The notion of inhibiting renin to lower blood pressure and its sequellae was not lost on pharmacologists, and early attempts were made at developing nonimmunological renin inhibitors [11]. The history of this chapter is interesting, fraught with failure, and only recently crowned with success. A temporally better approach turned out to be inhibition of the angiotensin-converting enzyme (ACE). Skeggs and colleagues had shown by their work that conversion of Ang I to Ang II was necessary to increase blood pressure. ACE was found to be largely tissue-bound and particularly abundant in the pulmonary vascular bed. The enzyme is a Zn-containing matrix metalloproteinase. Ferreira made the keynote observation that *Bothrops jararaca* venom contained a material that potentiated bradykinin [12]. Ondetti et al [13] determined the structure of the bradykinin-potentiating factors and also observed that the peptides diminished the increase in blood pressure otherwise generated by Ang I, notably the nonapeptide, teptrotide. Teprotide was subsequently widely studied in animals and man. Ondetti, Rubin, and Cushman subsequently designed a new class of specific ACE inhibitors [14]. ACE inhibitors ushered in a new age of cardiovascular pharmacotherapy. Another plausible target was the Ang II receptor (termed AT1 receptor). Pals, Masucci, Sipos, and Denning synthesized Sar-Ala-angiotensin, a peptide Ang II receptor blocker (ARB) better known as saralasin [15]. However, peptide ARBs proved to be not practicable. The development of modern ARBs led to the identification of Ang II receptor subtypes (AT1 and AT2 receptors) [16]. The development of 2-*n*-butyl-4-chloro-5-hydroxy-methyl-1-[(2'-(1H-tetrazol-5-yl)biphe nyl-4-yl) methyl] imidazole potassium salt ushered in another era of renin–angiotensin system inhibition [17].

The molecular cloning of a mouse submaxillary gland renin cDNA fragment by Pierre Corvol's group ushered in our knowledge of the renin gene [18]. That discovery also led to the appreciation of the mouse submaxillary renin [19], that in turn led to the first utilitarian transgenic model of hypertension [20]. The AT1 receptor was cloned 1 year later [21]. Thereafter, the progress is prodigious. The rest of the story is more or less contemporary and will unfold as part of this thematic issue of *Journal of Molecular Medicine*. Important parts include the cloning and characterization of the (pro)renin receptor, the discovery of ACE2, the identification of other angiotensins, already a theme in the 1978 symposium [21], and characterization of the Mas receptor. Also a fitting postlude to this introductory editorial is the long-awaited development of direct renin inhibitors. That chapter required the engineering of a novel animal model, inconceivable to the participants of the 1978 symposium. For me, a notable pleasure has been to personally know or have known some of the pivotal personalities mentioned here. They include Oscar Helmer, Myron Weinberger, George Pickering, Merlin Bumpus, Irvine Page, Sérgio Ferreira, Marc de Gasparo, Detlev Ganten, John Luetscher, John Vane, John Laragh, Jean Sealey, Jacques Genest, Tadashi Inagami, Kazuo Murakami, David Bohr, Joel Menard, and Pierre Corvol. I regret that I could not know Franz Gross personally; however, many of the participants of this symposium did. Gross would have surely livened the sessions!

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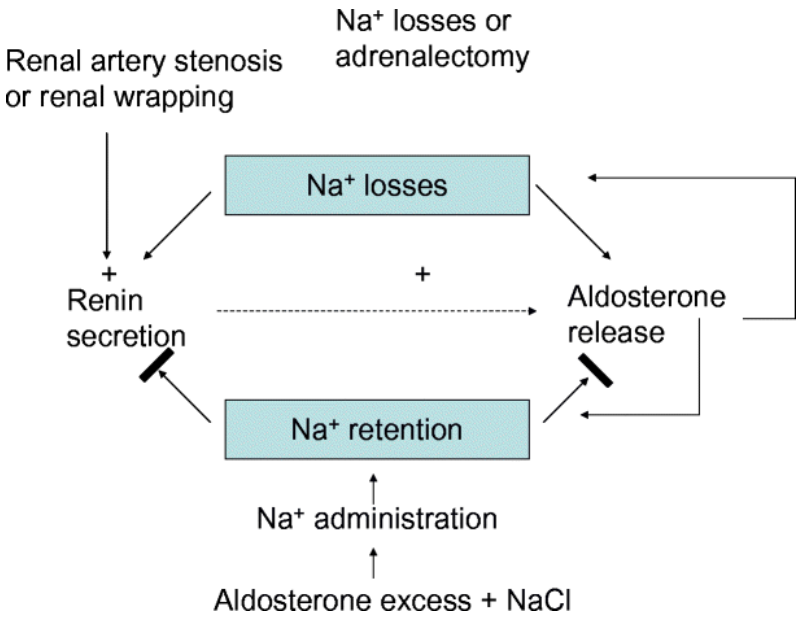

►Fig.1. Franz Gross' hypothesis from 1958 is shown. I have taken the liberty of translating his German into English. With remarkable insight, Gross reasoned that the signal between renin and aldosterone release (*dashed arrow*) had to be Ang II.