Evolutionary of Renin Angiotensin system and first developed ACE-I concepts: Two interwoven stories

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Angiotensin-converting enzyme (ACE) inhibitors were developed in the late 1960s using an extract of the venom of the Brazilian pit viper, Bothrop jararaca.

Intriguing question of why a snake's venom would contain an agent that blocks the RAAS.

- *Bothrops jararaca has* evolved in an environment with limited salt. The natural enemies of this Brazilian pit viper *(Bothrops jararaca)* also has evolved under similar environmental pressure , Human being also has developed under evolutionary pressure of salt deprived environment.

- In the 1960s and 1970s, anthropologist *Napoleon Chagnon* and the geneticist *James Neel*, extensively studied a tribe ,located in northern Brazil and southern Venezuela this tribe entitled Yanomamo, are hunter-gatherers emerged as one of the most primitive, culturally intact tribes in existence in our time.
- The traditional Yanomami diet is very low in edible salt. Their blood pressure is characteristically among the lowest of any demographic group.

- Neel's group focused on the Yanomamo's '*no salt culture*' and, in 1975, reported the mean blood pressures(BPs), plasma renin activities (PRAs), and urinary aldosterone excretion levels from a Yanomamo sample population. The mean systolic and diastolic BP, across 10-year age groups, ranged from 93.2–108.4 and 58.6–69.4 mmHg, respectively. Beside of this low BPs they had high renin activity and aldosterone levels.

- These hunter-gatherers, like other terrestrial animals living in a low-salt environment, had evolved a RAAS to conserve salt and maintain their BPs at livable levels. Their elevated renin and aldosterone levels were appropriate evolutionary responses to an environment with sparse salt.

- Salt only became a staple of the human diet after the emergence of agriculture to enable food preservation. In the Paleolithic (10,000 B.C) in pre-agricultural period, humans consumed less than one-fourth of the salt that modern.
- In pre-agricultural era human circulation was relied on RAAS-dependent norm tension to ensure adequate blood flow to all organs

- Circulatory need of terrestrial animals to a hyperactive RAAS , led the pit viper(Bothrops jararaca) to conserve an efficient killing mechanism that targeted their enemies hemodynamic vulnerabilities.

- The bradykinin potentiating factor (BPF) that would be the first discovered ACE-I in essence, is the viper's weapon of choice that targets the ACE dependent hemodynamic.as early human circulatory physiology had the same voulnerablity.

Sergio Henrique Ferreira (1934–2016)

- He isolated from the venom of Brazilian viper, a factor that prevents bradykinin degradation , first named it; bradykinin potentiating factor (BPF). Later they showed BPF would also inhibit the conversion of angiotensin I to angiotensin II by ACE and realized that it is an ACE inhibitor. Captopril was the first ACEI that produced.